

Draft for consultation

Clinical Guideline

Breast cancer (advanced): diagnosis and treatment

Evidence Review

Draft for consultation

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Chapter 2 – Presentation and Diagnosis

2.1 Investigations for (1) assessing disease extent and (2) monitoring the response to treatment, including positron emission tomography (PET)

2.1.1 Assessing the disease extent

Short summary

Two systematic reviews (Isasi *et al.*, 2005 and Shie *et al.*, 2008) and fifteen small comparative studies or case series (Abe *et al.*, 2005, Althoefer *et al.*, 2001, Bradley *et al.*, 2000, Bristow *et al.*, 2008, Cook *et al.*, 1998, Engelhard *et al.*, 2004, Eubank *et al.*, 2001, Eubank *et al.*, 2004, Fueger *et al.*, 2005, Haubold-Reuter *et al.*, 1993, Kamby *et al.*, 1987, Nakai *et al.*, 2005, Schirmeister *et al.*, 1999, Schmidt *et al.*, 2008 and Ternier *et al.*, 2006) formed the evidence base for the topic on imaging to determine disease extent. Other than the reviews, papers were generally of poor to medium quality and many were retrospective studies.

MRI and FDG-PET were equal to or better than scintigraphy in visualising bone metastases, other than osteoblastic lesions, but whole body MRI was better than FDG-PET at detecting distant metastases particularly in abdominal organs, brain and bone. MRI also detected previously unidentified metastases, including those that were non-skeletal and, in one study, the treatment plan was changed accordingly in ~43% of patients.

CT had a high diagnostic value in detecting local breast cancer recurrence and, when the field was extended to include the pelvis, also had a higher diagnostic accuracy in detecting bone metastases than scintigraphy.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Individuals with metastatic breast cancer requiring an assessment of disease extent (most commonly at diagnosis of metastatic disease)	<ul style="list-style-type: none"> • Plain chest x-ray, liver ultrasound & bone scintigraphy • CT - chest/pelvis/abdomen ± bone scintigraphy • MRI • PET-CT 	Each with each other	<ul style="list-style-type: none"> • Ability to assess disease extent • Ability to make treatment decisions

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

All study participants had breast cancer and most had metastatic disease but in some studies women with all stages of cancer were accepted on the basis that many had suspected metastases either as a result of patient reported symptoms or from other clinical findings. Papers concerning the staging of locoregional or metastatic disease were included as being relevant to 'assessing the disease extent'. The majority of papers either reported the sensitivity, specificity and accuracy of the imaging method under consideration or provided enough data for these

parameters to be calculated. In most studies the reviewers of the scanned images in question were blinded to the clinical findings, follow-up or to the results of other imaging.

With one exception, the studies in this summary are generally of poor to medium quality, being small comparative studies or case series, many of them retrospective. There were many more studies identified in the first screen of the available literature but most had patient numbers <10 and these were excluded as being of no evidential value – a stance adopted by the authors of the systematic review (Isasi *et al.*, 2005) who also excluded such papers.

The efficacy data, where available, are summarised in a table (Table 2.1.1.1) below.

Bone scintigraphy

There were seven papers studying the efficacy of bone scintigraphy versus either MRI (Haubold-Reuter *et al.*, 1993, Althoefer *et al.*, 2001 and Engelhard *et al.*, 2004) or PET scanning (Cook *et al.*, 1998, Schirrmester *et al.*, 1999, Abe *et al.*, 2005 and Nakai *et al.*, 2005) in the detection of bone metastases. These were all case series, four of which were retrospective and three prospective. The total number of patients was 299.

Three radionuclides were used: 99m technetium hydroxymethylene diphosphonate (99m Tc-HDMP), 99m technetium dicarboxypropane diphosphonate (99m Tc-DPD) and 99m technetium methylene diphosphonate (99m Tc-MDP).

The range of the sensitivity of scintigraphy across these studies was from 78.2% to 100%, the specificity from 77.8% to 100% and the range of accuracy from 79.8% to 93.8%.

Bone scintigraphy was not shown to be superior for visualising bone metastases compared with either MRI or FDG-PET, except when it came to osteoblastic lesions, which have lower metabolic activity.

MRI

There were four papers about MRI, three of them in comparison with bone scintigraphy (as above) and one retrospective study on MRI alone when used to determine the extent of disease in the axilla and to identify other areas of metastatic disease (Bradley *et al.*, 2000). As a result of these MRI findings the treatment plan was changed in 45/105 patients.

The total number of patients for this topic was 248. The range of sensitivity across all studies was 85% to 98.1%, specificity was 77.7% to 100% and accuracy from 81.3% to 98.9%. MRI was found to be superior to bone scintigraphy for the detection of bone metastases, particularly in the axial skeleton. The added advantage over scintigraphy was the ability of MRI to pick up unexpected, non-skeletal lesions although the expense of this technique might prohibit its use as a screening tool.

Bradley *et al.* (2000) also looked at the benefit of gadopentate dimeglumine (Gd-DTPA) as a contrast enhancement and determined that the sensitivity but not specificity or accuracy was improved.

FDG-PET

The greatest quantity of evidence for this topic concerned 18F fluorodeoxyglucose used with PET scanning (FDG-PET) in the imaging of breast metastases. Four papers detailed the comparison between this method and scintigraphy (as above) in the detection of bone metastases. FDG-PET was found to be better than bone scintigraphy for identifying additional lesions in patients known to have bone metastases by Schirrmester *et al.* (1999) but not significantly different from

scintigraphy in all respects other than the detection of osteoblastic lesions at which scintigraphy was superior (Nakai *et al.*, 2005).

There was a moderate quality, up to date systematic review on the use of FDG-PET to visualise breast cancer recurrence and metastases (Isasi *et al.*, 2005) and three other smaller studies, all retrospective case series. Since the patient number in the systematic review is >800, the total patient number for this modality is >1168.

The systematic review (Isasi *et al.*, 2005) collated data from 18 studies of FDG-PET used to detect the presence of breast cancer recurrence or metastases. They found that compared to MRI, FDG-PET showed higher sensitivity but lower specificity and when compared to CT, FDG-PET showed both a higher sensitivity and specificity. The quality of the review was hampered by the standards of the studies within it, half of which were low patient number retrospective case series. The authors' definition of 'breast cancer and metastases' was not further qualified and hence it was not immediately clear to what type of metastases they might be referring. However, an examination of some of the papers included in this review suggests that the metastases were of the body as a whole. Additionally, the authors of the review searched only Medline and may have missed other important sources of data.

Eubank *et al.* (2001) compared the efficacy of FDG-PET versus CT in identifying tumour recurrence in the ipsilateral breast or nodes and concluded that FDG-PET was superior to current methodology in nodal staging. The same group presented a later study looking at FDG-PET scanning for breast metastases in the whole body (Eubank *et al.*, 2004) and again concluded that FDG-PET had superior sensitivity over conventional imaging in identifying nodal disease and also distant metastases. Fueger *et al.* (2005) undertook a retrospective study comparing FDG-PET with PET combined with CT for breast cancer staging and found that combined imaging had a slight (but non-significant) advantage in re-staging breast cancer but was better than FDG-PET imaging alone at detecting osteoblastic bone lesions.

Study	No. of pts	Imaging modality	Area	Sensitivity %	Specificity %	Accuracy %
Nakai <i>et al.</i> , 2005	55	FDG-PET	bone	80.0	88.2	83.1
Abe <i>et al.</i> , 2005	44	FDG-PET	bone	100	96.7	97.7
Fueger <i>et al.</i> , 2005	58	FDG-PET	breast	84.8	72	79.3
Isasi <i>et al.</i> , 2005	>800	FDG-PET	breast	90.3	87.3	86
Eubank <i>et al.</i> , 2004	125	FDG-PET	whole body	94	91	92
Eubank <i>et al.</i> , 2001	73	FDG-PET	breast & nodes	85	90	88
Eubank <i>et al.</i> , 2001	73	CT	breast & nodes	40	85	63
Fueger <i>et al.</i> , 2005	58	PET/CT	breast	93.9	84	89.7
Nakai <i>et al.</i> , 2005	55	scintigraphy	bone	78.2	82.4	79.8
Abe <i>et al.</i> , 2005	44	scintigraphy	bone	78.6	100	93.2
Althoefer <i>et al.</i> , 2001	81	scintigraphy	bone	87	100	91.4
Engelhard <i>et al.</i> , 2004	22	scintigraphy	bone	83.3	80	81.8

Haubold Reuter <i>et al.</i> , 1993	40	scintigraphy	bone	100	77.8	93.8
Altehoefer <i>et al.</i> , 2001	81	MRI	bone	98.1	100	98.8
Engelhard <i>et al.</i> , 2004	22	MRI	bone	91.7	90	90.9
Haubold Reuter <i>et al.</i> , 1993	40	MRI	bone	82.6	77.7	81.3
Bradley <i>et al.</i> , 2000	59	MRI	axilla & other	85	98	90

Table 2.1.1.1 Efficacy data for all studies where this information was given or could be extracted.

The range of sensitivity across all studies was between 80% and 100%, specificity was between 72% and 96.7% and accuracy from 79.3% to 97.7%.

Ultrasonography

There was just one large, but rather dated (patients recruited in 1983) prospective case series study of liver ultrasonography (Kamby *et al.*, 1987) which recommended ultrasound as part of a larger package of tests to determine the presence of breast metastases in the liver.

Other imaging modalities

There were no studies identified on the use of plain chest X-ray, or CT 'packages' for the ability to assess disease extent.

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Evidence tables

Question: Imaging to assess the extent of disease
Created by: Karen Francis on 22/01/2007

Altehoefer <i>et al.</i> (1997)
Design: Prospective comparative study (diagnosis, screening), evidence level: 3 Country: Germany
Inclusion criteria: Less than 2 months between MRI and scintigraphy.
Exclusion criteria: Treatment with chemotherapy or radiotherapy in the period between the two imaging events.
Population: Number of patients = 81.
Interventions: 1] Whole body scintigraphy (Tc-99m DPD) 2] MRI (T1- and T2-weighted spin or turbospin echo)
Outcomes: Comparison of the efficacy of bone scintigraphy vs MRI for detecting and staging bone metastases secondary to BC.

<p>Follow up: -</p>
<p>Results: 47/81 patients had MBC and of these 29 were known to have bone metastases.</p> <p>Bone metastases were assumed to be present in patients with both a positive MRI and scintigram. Similarly, a negative finding in both imaging modalities was accepted as indicating an absence of metastases. Where scan results differed, the matter was resolved by histology after surgery, clinical follow-up or further MRI or scintigraphy.</p> <p>Scintigraphy (and MRI) positively identified bone metastases in 46 patients. Scintigraphy also identified 1 patient with a sternal metastasis which was not detected by MRI.</p> <p>Scintigraphy (and MRI) revealed the absence of bone metastases in 27 patients. Scintigraphy failed to show spinal metastases in 7 patients (3 of which had stage IV MBC) which were correctly visualised by MRI. These were confirmed as positive by clinical follow-up (n = 6) or histology (n = 1.)</p> <p>MRI had a specificity of 98.1%, a sensitivity of 100% and a test accuracy of 98.8%</p> <p>Scintigraphy had a specificity of 87%, a sensitivity of 100% and a test accuracy of 91.4%</p> <p>The extent and location of metastases were concordant in 22/46 patients. In 9 patients, MRI detected a higher number of metastases than scintigraphy and in 15 patients the presence or absence of metastases in any particular location differed between the two methods. In 26 patients, scintigrams revealed the presence of additional sites of metastases.</p> <p>Local RT or surgery was indicated in 10 patients with metastases seen only with MRI, in 20 patients that had positive results for both scans and in 6 patients with metastases visualised only with scintigraphy.</p>
<p>General comments: This paper describes a retrospective study. BC patients that had received MRI for staging, follow-up or evaluation of bone pain or neurological symptoms (between December 1992 and January 1999) and who met the inclusion criteria for the study were enrolled. Patients received whole body scintigraphy and the images were compared with those of MRI.</p> <p>Scintigrams were read by 2 independent nuclear physicians who were blinded to MRI outcome. Similarly MRI scans were evaluated by 2 radiologists blinded to the results of the scintigram. Disagreements were resolved by consensus.</p> <p>Authors conclude that MRI is more sensitive than scintigraphy in the detection of bone metastases, particularly in the axial skeleton as peripheral-only metastases are rare.</p>
<p>Engelhard <i>et al.</i> (2004)</p>
<p>Design: Prospective comparative study (diagnosis, screening), evidence level: 3 Country: Germany</p>
<p>Inclusion criteria: Referral for MRI on the basis of pain, high tumour marker levels or suspected metastases by other imaging methods. Informed written consent</p>
<p>Exclusion criteria:</p>

None stated
<p>Population: Number of patients = 22, age range 53 to 87 years, mean age = 63 years.</p>
<p>Interventions: All patients received both: 1] Scintigraphy with 99m Tc-MDP 2] Whole body MRI with T2-weighted turbo-spin echo (TSE) and short tau inversion recovery (STIR) pulse sequence, using a moving table at 6 different positions. After each coronal measurement, a sagittal T1-weighted pulse sequence was performed. Procedure lasted 20min.</p>
<p>Outcomes: Comparison of efficacy of whole body MRI with moving table versus scintigraphy in the detection of bone metastases due to breast cancer.</p>
<p>Follow up: 1 year</p>
<p>Results: 10/22 patients scored negative on the presence of metastases after clinical and imaging follow-up. 4/22 scintigraphs were grade 2 (unclear) compared with 2/22 MRI scans.</p> <p>MRI: sensitivity = 91.7% specificity = 90% and test accuracy = 90.9%. Scintigraphy: sensitivity = 83.3% specificity = 80% and test accuracy = 81.8%</p> <p>Additional metastases were identified by MRI: lung (2), lymph node (1), pleural effusion (3) and atelectasis of the lung (1).</p>
<p>General comments: Patients were recruited prospectively and received scintigraphy and MRI within 3 weeks of each other.</p> <p>Bone scintigraphy and MRI images were analysed prospectively by two investigators independently from the results of the other procedure. Differences were resolved through consensus. Bone changes were scored as 1 (benign), 2 (unclear) or 3 (malignant). Unclear readings were followed up for 1 year with at least one follow-up study i.e. MRI, CT, radiographs or scintigraphy before being graded either 3 or 1. Criteria for assessing these grades are thoroughly reported.</p> <p>Whilst thoroughly conducted and reported, this study is of low patient number and so the results must be viewed with caution.</p> <p>Authors regard the ability of MRI to detect non-skeletal metastases an advantage over scintigraphy particularly given the short procedure and room time (40 min) but the relative expense of MRI may prohibit its use as a screening tool in patients other than those already believed to have distant metastases.</p>

Haubold-Reuter <i>et al.</i> (1993)
<p>Design: Prospective comparative study (diagnosis, screening), evidence level: 3 Country: Switzerland</p>
<p>Inclusion criteria: Informed consent Histologically proven primary tumour</p>

Exclusion criteria: -
Population: Number of patients = 40, age range 41 to 81 years.
Interventions: All patients underwent all three of the following examinations: 1] Bone scintigraphy (99m Tc-DPD) 2] Bone marrow scintigraphy (99m Tc-labelled monoclonal antibodies against a non-specific, cross-reacting antigen found on neutrophil granulocytes) 3] MRI (T1-weighted SE sequences and FSE T2-weighted sequences)
Outcomes: Comparison of the efficacy of three methods of imaging suspected bone metastases (sensitivity and specificity).
Follow up: One year of clinical and imaging follow-up after baseline imaging.
Results: Bone scan findings were confirmed by plain film, CT and, if relevant, patient interview. Bone marrow scans were compared with X-rays and MRI by the use of T1 and T2-weighted images. In 32 patients there were 139 metastases identified by the reference standard - 106 in the axial skeleton and 33 in the periphery. Bone scan identified 104/139 metastases (74.8%), 71/106 in the axial skeleton and 33/33 in the periphery. 30/32 patients were correctly classified as tumour stage M1 with sensitivity of 100% and specificity of 77.8%. Test accuracy = 93.8%. Bone marrow scan identified 81/139 metastases (53.8%), 75/106 in the axial skeleton and 6/33 in the periphery. 20/32 patients were correctly staged as M1 with sensitivity of 82.6%, specificity of 11.1% and test accuracy of 62.5%. MRI detected 106/139 metastases (76.3%), 106/106 in the axial skeleton and none in the periphery (due to limited field of view). 26/32 patients were correctly classified as M1 with 82.6% specificity, 77.7% sensitivity and test accuracy of 81.3%.
General comments: This paper describes a small comparative study of three imaging techniques, all compared against a reference standard. The ideal gold standard would have been to have had biopsy material with which to determine disease extent but this is not obviously not feasible. The reference standard in this study was a period (1year) of clinical follow-up together with repeated imaging of areas of study. Of 40 patients, 15 were women with MBC. Data were not presented by sub-group. Imaging examinations were read by 2 radiologists and 2 nuclear medicine specialists. All relevant information (including clinical notes and other imaging results) were freely available. Differences were resolved by consensus. The authors conclude that, since many patients first present with peripheral metastases, bone scan supported by plain X-rays yield sufficient information to correctly assess the presence of bone metastases whilst MRI should be used as an adjunct given the lesion by lesion sensitivity. Bone marrow scan could not distinguish between metastases and fatty bone marrow degeneration and has a similarly low field of vision but with less specificity.

Nakai <i>et al.</i> (2005)
Design: Retrospective comparative study (diagnosis, screening), evidence level: 3 Country: Japan
Inclusion criteria: Evidence of metastatic bone disease defined by MRI No previous treatment to bone lesions Written informed consent
Exclusion criteria: None stated
Population: Number of patients = 55, age range 29 to 83 years, mean age = 59 years.
Interventions: Patients were given FDG-PET and 99m Tc HMDP within a month of each other. CT scan was also obtained in order to classify metastases as blastic, lytic, mixed or invisible. Bone scintigraphy: 740MBq of 99m Tc HMDP was given by iv injection and images taken after 2hr. FDG-PET: After 4hr fasting, patients were given 250-300MBq of 18F FDG and then scanned 60min later.
Outcomes: Comparison of the sensitivity and specificity of FDG-PET and bone scintigraphy in the evaluation of osteoblastic bone metastases.
Follow up: -
Results: Bone scintigraphy revealed 99m Tc-HMDP uptake at 49/55 sites but was false positive at 6 sites and false negative at 12 sites. FDG-PET revealed FDG uptake at 48/55 sites but was false positive at 4 sites and false negative at 11 sites. Sensitivity of bone scintigraphy = 78.2% Specificity of bone scintigraphy = 82.4% Accuracy of bone scintigraphy = 79.8% Sensitivity of FDG-PET = 80.0% Specificity of FDG-PET = 88.2% Accuracy of FDG-PET = 83.1% Visualisation rates bone scintigraphy: Blastic: 18/18 (100%) Lytic: 7/10 (70%) Mixed: 16/19 84.2% Invisible: 2/8 (25%) Visualisation rates FDG-PET: Blastic: 10/18 (55.6%) P< 0.0781 Lytic: 10/10 (100%) nsd

Mixed: 18/19 (94.7%) nsd
 Invisible: 7/8 (87.5%) P< 0.0313

The visualisation rate of FDG-PET for the blastic type of lesion was significantly lower than that of scintigraphy (P<0.0313) but other visualisation rates were nsd.

General comments:

This paper describes a study in which 55 patients, all of whom had a definitive diagnosis of bone metastases from breast cancer (by MRI) received both bone scintigraphy and FDG-PET within 4 weeks of one another.

Results of scanning and scintigraphy were evaluated and compared independently by two board certified nuclear physicians.

Kamby *et al.* (1987)

Design: Prospective case series (diagnosis, screening), evidence level: 3

Country: Denmark

Inclusion criteria:

Recurrent breast cancer

Exclusion criteria:

Concurrent other primary cancers

Age >75 years due to rigor of treatment schedule

Population:

Number of patients = 394, age range 28 to 75 years.

Interventions:

Patients received liver ultrasound. Focal processes identified at the time were biopsied in patients that did not already have a diagnosis of liver metastases.

Outcomes:

One of the outcomes of this study was to assess the value of ultrasonography in patients with first recurrence of breast cancer.

Follow up:

History, physical examination, blood tests (haemoglobin, leukocytes, thrombocytes, serum calcium, bilirubin, alkaline phosphatase, aspartate aminotransferase and lactate dehydrogenase), chest X-rays and bone scintigraphy (after 1984).

Results:

Ultrasound showed liver metastases in 59/394 (15%) patients. Only 39/59 of these patients had a biopsy taken to compare with these findings. 36/39 (92%) had metastases confirmed by pathology and 3 patients were negative.

General comments:

This is old (patients recruited from 1983) prospective study which included liver ultrasonography as part of a comprehensive package of tests to determine the presence or otherwise of metastatic disease in patients with first recurrence of breast cancer. There is very little evidence towards the efficacy of this imaging technique in this particular paper.

Schirrmeister *et al.* (1999)

Design: Prospective case series (diagnosis, screening), evidence level: 3

Country: Germany

Inclusion criteria: Patients with or at a high risk of bone metastases from breast cancer.
Exclusion criteria: None stated
Population: Number of patients = 34, age range 37 to 75 years, mean age = 52 years.
Interventions: PET scanning of the skeletal trunk after iv injection of fluoride ion (F-18) compared with bone scintigraphy with 99m-Tc methylene diphosphonate (12 patients had additional SPECT). These imaging studies were performed on all patients within 3 weeks of one another. Reference standard: MRI of the head, spine and pelvis with T1 weighted spin echo and fat suppressed T2 weighted sequence (n=28). Some patients had gadolinium enhancement. Patients were also assessed by means of CT scan (n = 4) and planar X-ray (n = 17).
Outcomes: Comparison between PET and scintigraphy in the detection of bone metastases due to breast cancer with MRI as reference standard. Lesions were scored using a 5-point scale as: definitely metastatic (2) probably metastatic, (3) equivocal, (4) probably not metastatic and (5) definitely not metastatic. P <0.05 was considered significant.
Follow up: Clinical management was changed in 4/34 patients as a result of PET scan results and was influenced in a further 6.
Results: F-18 PET correctly identified the 6 patients with known bone metastases and also highlighted additional foci in 5/6 of these patients. Of 28 patients previously unknown to have bone metastases PET correctly identified 16/17 as 'positive' for metastases and 11 as 'negative'. One result was 'equivocal' but was shown to be 'positive'. There were no false 'negatives' or 'positives'. The area under the ROC curve was 1. Scintigraphy correctly identified the 6 patients with known bone metastases and also highlighted additional foci in 2/6 of these patients. Of 28 patients previously unknown to have bone metastases scintigraphy correctly identified 5/17 as 'positive' for metastases and 11 as 'negative'. Seven results were 'equivocal' of which 3 were 'positive' and 4 'negative'. Five results were considered 'negative' of which 3 were actually 'positive'. Hence there were 3 false 'positives' and 2 false 'negatives'. The area under the ROC curve was 0.82.
General comments: ROC analysis was used to define the outcomes since these were not dichotomous. Bone scans and PET scans were assessed separately by two pairs of experienced nuclear medicine physicians each blinded to the other results. MRI scans and other diagnostic images were assessed by two diagnostic radiologists. Differences were resolved by discussion and consensus. Patients were deemed not to have metastases when none of the imaging revealed suspicious lesions or when lesions suggested by PET and/or scintigraphy were shown to be negative by reference methods. Authors concluded that the extent of disease was 'strongly underestimated' in 11/17 patients by bone scintigraphy and that PET was 'optimally accurate' in terms of staging and 'clearly superior' to BS in terms of describing the extent of metastatic disease.

Abe <i>et al.</i> (2005)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: Japan
Inclusion criteria: Women with breast cancer No prior aggressive chemotherapy, no radiotherapy to bone lesions before study (endocrine therapy allowed)
Exclusion criteria: None stated.
Population: Number of patients = 44, age range 35 to 81 years, mean age = 56 years.
Interventions: Patients were given 18 FDG-PET and 99m Tc HMDP within 0-69 days (mean 11.5 days) of each other. Bone scintigraphy: 740MBq of 99m Tc HMDP was given by iv injection and images taken after 4hr. 18 FDG-PET: After at least 4hr fasting, patients were given a mean of 219MBq of 18 FDG and then scanned after 60min. Confirmatory tests included plain radiography, CT, MRI and biopsy. The bone scintigraphy and 18 FDG-PET scans were reviewed retrospectively by three nuclear medicine physicians blinded to clinical information. Two diagnostic radiologists evaluated the plain radiographs and CT scans and classified the metastases by body region and as either osteoblastic or osteolytic lesions.
Outcomes: Comparison of bone scintigraphy and 18 FDG-PET in detecting bone metastases in breast cancer patients.
Follow up: At least 6 months.
Results: Bone metastases were found in 14/44 women, confirmed by biopsy (n = 2), CT (n = 5) and MRI (n = 7). Analysis by patient for 99m Tc-HMDP bone scintigraphy: 11/14 true positives were detected (sensitivity = 78.6%) 30/30 true negatives were detected (specificity = 100%) accuracy = 41/44 = 93.2% Analysis by patient for 18 FDG-PET: 14/14 true positives were detected (sensitivity = 100%) 29/30 true negatives were detected (specificity = 96.7%) accuracy = 43/44 = 97.7% Combined imaging per patient: 14/14 true positives were detected (sensitivity = 100%) 29/30 true negatives were detected (specificity = 96.7%) accuracy = 43/44 = 97.7%

A reanalysis of the data grouped by body region (n = 187) showed a total of 45 regions were positive for bone metastasis:

99m Tc-HMDP bone scintigraphy:

36/45 true positives were detected (sensitivity = 80.0%)

140/142 true negatives were detected (specificity = 98.6%)

accuracy = 176/187 = 94.1%

18 FDG-PET:

38/45 true positives were detected (sensitivity = 84.4%)

140/142 true negatives were detected (specificity = 98.6%)

accuracy = 178/187 = 95.2%

Combined imaging per region:

44/45 true positives were detected (sensitivity = 97.7%)

138/142 true negatives were detected (specificity = 97.2%)

accuracy = 182/187 = 97.3%

Detection of osteoblastic (n = 19) and osteolytic (n = 26) lesions:

Osteoblastic:

99m Tc-HMDP bone scintigraphy = 17/19 (94.7%)

18 FDG-PET = 14/19 (73.7%)

Combined = 17/19 (94.7%)

Osteolytic:

99m Tc-HMDP bone scintigraphy = 19/26 (73.1%)

18 FDG-PET = 24/26 (92.3%)

Combined = 26/26 (100%)

General comments:

This retrospective study includes data from patients at all stages of breast cancer: stage 1 (n = 16), stage 2a (n = 12), stage 2b (n = 2), stage 3 (n = 3), stage 4 (n = 4) or unknown (n = 7).

There was no significant difference in efficacy between imaging modalities or between either or them and combined imaging when examining data on a patient basis. On a region basis, the sensitivity and accuracy of combined imaging statistically outweighed that of either of the individual components.

The authors conclude that whilst there is little to choose between methods for imaging bone metastases, 18 FDG-PET is superior to bone scintigraphy in the detection of osteolytic metastases and the reverse is true with osteoblastic metastases.

Bradley *et al.* (2000)

Design: Retrospective case series (diagnosis, screening), evidence level: 3

Country: United Kingdom

Inclusion criteria:

Histologically proven breast cancer (not metastatic)

Previous MRI examination for symptoms related to the ipsilateral axilla.

Exclusion criteria:

None stated

Population:

Number of patients = 105, age range 33 to 91 years, mean age = 55 years.
Interventions: T1 weighted spin echo and T2 weighted turbo spin echo sections of 6mm with occasional enhancement (n = 38) with iv gadopentate dimeglumine (Gd-DTPA). Reviewers documented the findings of each image in respect of features due to malignancy of the axilla, sites of metastatic disease elsewhere in the image (including brain, lung, liver, muscles and lymph node enlargement) and features due to treatment effect. Findings were classified as 'recurrent axillary tumour', 'metastatic tumour', 'treatment induced fibrosis' or 'normal'. Clinical correlation was on the basis of case note review. Patients were classified as 'dead', 'progressive disease', 'stable disease' or 'free of tumour'.
Outcomes: To compare MRI image results with clinical evaluation and outcomes a year later and assess the efficacy of MRI in the differentiating between metastatic disease and the effects of previous treatment for cancer in the axilla.
Follow up: At the time of MRI assessment, patients had undergone a median follow-up of 669 days for those 63 patients still living and 364 days for those patients who had died in the interim. All patients had T1W axial and T2WTSE coronal images. At least 12 months after MRI examination.
Results: Clinically, 54 patients had axillary tumour including 48 assessed by MRI. 6/54 were incorrectly assessed by MRI as having treatment effect (n = 4) or as normal (n = 2) (sensitivity of 89%, specificity of 100% and accuracy of 94%). Clinically, 59 patients were positive for metastatic disease outside the ipsilateral breast and axilla, 50 of them assessed by MRI. 9/54 were incorrectly assessed by MRI as treatment effect (n = 4) or normal (n = 5) (sensitivity of 85%, specificity of 98% and accuracy of 90%). Clinically, 27 patients were diagnosed to have treatment effects and 22 patients were clear of disease. In 38 patients who had received Gd-DTPA enhancement diagnosis was altered in 15 (39%) and improved diagnostic confidence in 12 (31%). Sensitivity for detecting axillary tumour was improved from an original 42% to 73% in those patients. Specificity remained at 100% and accuracy increased from 61% to 83%. As a result of the MRI findings treatment was affected in 45 patients, 43 of whom had been diagnosed with recurrent tumour.
General comments: MRI examinations were assessed jointly by two radiologists without clinical information other than the side of the body concerned. Gd-DTPA images were assessed twice, with and without enhancement, and a time interval of at least 6 months between viewings.
Cook <i>et al.</i> (1998)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United Kingdom
Inclusion criteria:

History of breast cancer with evidence of bone metastases
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 23, age range 29 to 70 years, mean age = 52 years.</p>
<p>Interventions: Patients were given 18 FDG-PET and 99m Tc MDP within 8 weeks of each other.</p> <p>Bone scintigraphy: 550MBq of 99m Tc HDMP was given by iv injection and images taken after 2hr.</p> <p>18 FDG-PET: After 6hr fasting, patients were given 350MBq of 18 FDG and then scanned later. 16 patients received half-body emission and localised scans whilst 7 received localised scans only.</p> <p>Confirmatory tests included plain radiography (n = 17), CT (n = 10), MRI (n = 6) or biopsy (n = 2). Lesions were graded as either lytic, sclerotic or mixed by two independent observers from plain films (n = 16) or CT scans (n = 4). 2 patients were not assessable by these means.</p>
<p>Outcomes: Comparison of the sensitivity of 18 FDG-PET and bone scintigraphy to detect osseous metastases.</p> <p>Quantitation of 18 FDG uptake was measured in osteolytic and osteoblastic metastases.</p>
<p>Follow up: -</p>
<p>Results: 23/23 patients had metastatic disease confirmed by other imaging techniques or by bone biopsy.</p> <p>Of the 16 patients that had received a half-body PET scan and localised scans, the results with 18 FDG were 0-61 lesions visualised per patient (mean 14.1) compared with 0-38 lesions detected with bone scintigraphy (mean 7.8)(P < 0.01). 3 patients had sclerotic disease, 3 had mixed disease, 8 had lytic disease and 2 were not classified</p> <p>18 FDG detected fewer bone metastases than scintigraphy in a subgroup of patients with osteoblastic disease. Higher standardised uptake values (SUV) were noted for osteolytic than osteoblastic disease (mean 6.77 vs 0.95 P < 0.01).</p> <p>20 patients had radiologically classifiable disease. Of these, 6 patients had sclerotic disease, 5 patients had mixed disease and 9 patients had lytic disease. The mean SUV for these patients were 0.95, 3.64 and 6.77 respectively.</p>
<p>General comments: This paper describes a small, possibly retrospective, study of 23 women with bone metastases that had 18 FDG-PET scan and bone scintigraphy within 8 weeks of one another to assess extent of disease.</p> <p>21/23 women had progressive metastatic disease and 10 received endocrine therapy which may have ended as little as 1 month before imaging.</p> <p>Authors conclude that 18 FDG-PET is superior to bone scintigraphy in detecting osteolytic metastases however osteoblastic metastases show lower metabolic activity and are therefore harder to detect with PET.</p>

Eubank <i>et al.</i> (2001)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United States
Inclusion criteria: Permission to review medical records All breast cancer patients referred for FDG-PET
Exclusion criteria: None stated
Population: Number of patients = 125, age range 23 to 85 years, mean age = 50 years.
Interventions: After fasting for at least 4hr (typically 6-12hr) patients received between 244-400MBq iv injection of FDG and were scanned after 45 min. Patients with suspected widespread disease received a whole body scan and those suspected of having loco-regional disease had a limited torso survey from the neck to the bottom of the liver.
Outcomes: To assess the impact of FDG-PET in evaluating the extent of disease and the influence it might have on the patient management plan. To determine the impact on disease evaluation, imaging results were compared with findings at clinical examination and on other imaging results including CT, MRI and bone scans which had been performed prior to PET scanning. The mean interval between CT and PET scans was 17.9 days (range: 0-95 days). Impact of FDG was defined as either 'increased', 'decreased' or 'no change'. FDG results were confirmed by histopathology (n = 23) or follow-up imaging (n = 38). The method employed with the remaining 64 patients is not elaborated. To determine the influence of FDG-PET on patient management, subsequent treatment changes were graded as 'altered', 'supported' or 'no change'. 'Altered' treatment could be intra-modality' i.e. from chemotherapy to surgery or 'intra-modality' i.e. change of radiation field. Such influences were agreed by the treatment team of oncologists.
Follow up: Confirmation of FDG-PET findings was based on the period 2 months following the scan.
Results: FDG-PET was positive in 94 patients (75%), negative in 26 (21%) and equivocal in 5 (4%). The extent of disease was evaluated as increased (n = 54), decreased (n = 30) or no change (n = 41) in comparison with conventional imaging. FDG-PET showed a change in the disease extent more often in patients with loco-regional disease (P = 0.04). The predominant site of FDG uptake in patients with increased disease was in the nodal regions of the chest wall (71% of sites) compared with the viscera or skeleton. As a result of the FDG-PET image results, the management plan changed for 40 (32%) patients, supported the plan in 34 (27%) and made no difference in 51 (41%). The greatest impact was made on patients with loco-regional disease (17/39 patients) (P = 0.06 compared with all other patients). The least impact was made on patients with known metastatic disease who had been referred for evaluating disease extent. Patients receiving a scan to evaluate the response to treatment had their treatment altered or supported the most frequently.

23 patients had pathological confirmation of which 20 patients had true positive findings and there was one each of true negative, false negative and false positive. In the 38 patients whose findings were confirmed by follow-up imaging, 27 showed disease progression (true positive), 9 had true negative findings and 2 had false negative findings. The overall sensitivity of FDG-PET was 94%, specificity was 91% and accuracy was 92%.

General comments:

This paper describes a retrospective study of consecutive patients at a single institution that had received FDG-PET imaging for breast cancer between January 1998 and May 2002.

The extent of disease from FDG-PET findings was reviewed retrospectively from a prospective evaluation performed at the time of the scan by two or more nuclear medicine physicians. These results were compared with clinical data and conventional imaging. Overall interpretation was based on qualitative visual interpretation and comparison of the mean maximum SUV in positive sites of disease with normal background uptake. Findings were graded as 'positive', 'negative' or 'equivocal'.

Some (58%) patients were known to have positive axillary node status at the time of initial diagnosis.

The follow-up period of only 2 months in order to confirm or contradict the FDG-PET results seemed rather short and 51% patients had no other form of testing as a basis of comparison.

Fueger *et al.* (2005)

Design: Retrospective case series (diagnosis, screening), evidence level: 3

Country: United States

Inclusion criteria:

Patients with breast cancer and about whom there is sufficient clinical information to verify the disease status.

Exclusion criteria:

None stated.

Population:

Number of patients = 58, age range 29 to 80 years, mean age = 53 years.

Interventions:

Patients fasted for 6hr before being given 740MBq 18F FDG followed 60min later by PET scan using a Reveal PET/CT scanner. PET in 3D mode and whole body CT images were obtained. Images were taken from the base of skull to mid thigh. CT images were subsequently matched to PET data and the images were reconstructed.

Outcomes:

A comparison between PET alone and in combination with CT imaging to determine if the latter adds more information towards the successful staging of cancer in the breast.

PET/CT findings were verified by clinical follow-up, serum markers, independently acquired CT images, plain radiography, bone scans and mammography.

Follow up:

9 months +/- 4.4 months

Results:

33/58 patients had confirmed breast disease as determined by elevated tumour markers and positive imaging and/or an increase in the number and/or size of lesions during the follow-up period.

PET:

Correct disease status = 46/58 (79.3%)

Incorrect disease status = 12/58 (20.7%) with 7 false +ve results and 5 false -ve results.

Sensitivity = 84.8% specificity = 72% and accuracy = 79.3%

PET/CT:

Correct disease status = 52/58 (89.7%)

Incorrect disease status = 6/58 (18.3%) with 7 false +ve results and 5 false -ve results.

Sensitivity = 93.9% specificity = 84% and accuracy = 89.7%

The statistical significance between sensitivity PET vs PET/CT P = 0.32 (nsd)

The statistical significance between specificity PET vs PET/CT P = 0.32 (nsd)

The statistical significance between accuracy PET vs PET/CT P = 0.06 (nsd)

General comments:

This paper describes a retrospective case series of 58 breast cancer patients who received both conventional PET scan and PET/CT between August 2002 and November 2003.

Two nuclear medicine physicians evaluated the PET images and the same reviewers also interpreted the PET/CT results. These reviewers knew the patient diagnosis but not the disease status.

Reasons for false positives with either imaging modality include benign hyperplasia, pneumonia, fat necrosis and post-surgical changes. False negatives occurred in some cases of axillary lymph node metastasis and local recurrence of breast cancer.

It was concluded that FDG-PET alone was not a good technique for osteoblastic lesions but CT had an accuracy of 75% therefore the combination imaging should improve this overall.

Authors state that PET-CT can only be successfully evaluated after a careful interpretation of the CT data set.

Eubank *et al.* (2004)

Design: Retrospective case series (diagnosis, screening), evidence level: 3-

Country: United States

Inclusion criteria:

Patients with recurrent or metastatic breast cancer

Exclusion criteria:

None stated

Population:

Number of patients = 73, age range 26 to 75 years, mean age = 50 years.

Interventions:

All patients received a CT and FDG-PET scan within one month of each other. These images were obtained at several institutions.

Thoracic CT:

Full details of methodology are given where known but for 10 patients these details were not obtainable.

FDG-PET:

After fasting for 4hrs patients received an iv injection of between 6.6 to 10.8 mCi FDG and were imaged after 45 min.

Outcomes:

To compare the prevalence of suspected disease in the mediastinal and internal mammary nodes (IM) based on abnormal findings with FDG-PET versus conventional staging with CT.

In the home institute, prospective CT scans of 39 patients were reviewed by consensus of a fellow and a visiting radiologist who had access to FDG-PET scan results, where available. CT scans at outside institutions were reviewed by a single radiologist but it is not stated whether or not FDG-PET data were available to this person.

FDG-PET scans were reviewed by 2 or more non-independent nuclear medicine physicians who had access to CT scan results, where available.

An separate, independent review of CT scans was made for 63/73 patients by 2 blinded observers. For the remaining patients the scans could not be located (data not included in efficacy summary). Classification was 1 (definitely benign), 2 (probably benign), 3 (equivocal), 4 (probably malignant) and 5 (definitely malignant).

Follow up:

Confirmation of positive imaging results was obtained from histopathology and follow-up CT imaging for 33 patients and by FDG-PET for 7 patients. There are no details of other reference standards for the remaining 33 patients.

Results:

For the patients that had confirmation of results by histology or CT scanning (n = 33):

FDG-PET: sensitivity = 85% (95% CI: 73-97%)
FDG-PET: specificity = 90% (95% CI: 80-100%)
FDG-PET: accuracy = 88%

Prospective CT: sensitivity = 54% (95% CI: 37-71%)
Prospective CT: specificity = 85% (95% CI: 73-97%)
Prospective CT: sensitivity = 73%
Blinded interpretation of CT: sensitivity = 50% (95% CI: 33-67%)
Blinded interpretation of CT: specificity = 83% (95% CI: 70-96%)
Blinded interpretation of CT: accuracy = 70%

Including those patients whose results were confirmed by follow-up FDG-PET (total n = 40):

FDG-PET: sensitivity = 85% (95% CI: 74-96%)
FDG-PET: specificity = 90% (95% CI: 81-99%)
FDG-PET: accuracy = 88%

Prospective CT: sensitivity = 40% (95% CI: 25-55%)
Prospective CT: specificity = 85% (95% CI: 74-96%)
Prospective CT: sensitivity = 63%

Blinded interpretation of CT: sensitivity = 39% (95% CI: 24-54%)
Blinded interpretation of CT: specificity = 83% (95% CI: 71-95%)
Blinded interpretation of CT: accuracy = 61%

Mediastinal or IM abnormalities were present in 29/73 patients by FDG-PET and 17/73 patients by prospective CT. Mediastinal abnormalities were present in 16/73 patients by both imaging modalities. Findings by FDG-PET were concordant in 81%.

General comments:

This paper presents the results from a retrospective case series of 73 patients with metastatic or recurrent breast cancer who between March 1995 and May 1998 had received both whole body FDG-PET and chest CT scans.

The reviewers in most cases were not blinded to the results obtained by the other imaging method and in only 40/73 patients were the results confirmed by other means.

Isasi *et al.* (2005)

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: 1
Country: United States

Inclusion criteria:

Criteria for assessing the quality of included studies:

Technical Quality of FDG-PET

Spatial resolution < 11 mm

FDG uptake period ≥ 30 min

FDG dose ≥ 10 mCi

Acquisition time for emission scan specified

Attenuation correction performed

Participants studied in the fasting state

Positive test results defined according to specific criteria

Technical quality and application of the reference test or tests

Description of reference standard

Independence of test interpretation

FDG-PET readers blinded to the results of the reference test or tests

Clinical characteristics of the study sample described

Age, sex, number of patients enrolled, reason for performing PET

Cohort assembly

Participants enrolled prospectively

Individual patient used as unit of data analysis

Exclusion criteria:

Participants with hyperglycemia excluded

Population:

Number: n/k age range 14 to 89 years.

Interventions:

FDG-PET in the evaluation of breast cancer recurrence and metastases.

Outcomes:

Sensitivity and specificity of diagnostic tests in the detection of breast cancer recurrence and metastases.

Follow up:

-

Results:

18 papers were included in this analysis. 16 papers were patient-based (n = 808) and 2 papers were lesion-based (n = 1013) but the data were analysed separately. 7 studies were retrospective, 6 were prospective and 5 were indeterminate.

Patient-based data:

Median sensitivity = 92.7% (range: 56-100%)

Median specificity = 81.6% (0-100%)

True positive rate (sensitivity) = 90.3%
False positive rate = 12.7% (therefore specificity = 87.3%)
Test accuracy = 86%
Test for homogeneity = $P < 0.05$ (statistically significant).

Lesion-based data:

Median sensitivity = 91.7% (range: 57-97%)
Median specificity = 88.9% (79-96%)
True positive rate (sensitivity) = 85.1%
False positive rate = 6.9% (therefore specificity = 93.1%)
Test accuracy = 89.1%
Test for homogeneity = $P < 0.05$ (statistically significant).

When one patient-based study was excluded (with a sensitivity of only 55.5%) the overall diagnostic accuracy was raised to 88% and the test for heterogeneity was no longer significant ($P > 0.05$). The participants from the excluded study were selected on the basis of NOT having any evidence of metastatic disease and would therefore not fit the inclusion criteria for this question anyway.

Similarly, with lesion based studies, the exclusion of one study with very low sensitivity (56.5%) increased the overall diagnostic accuracy to 91% and the statistical heterogeneity to $P > 0.05$ (not significant). The excluded study had analysed a sub-set of data relating to bone metastases only.

After the exclusion of these studies the overall sensitivity was 90% and the specificity was 88%.

General comments:

Authors suggest that it is more clinically relevant to consider the findings for patient-based data rather than lesion-based data since the presence or absence of metastatic disease is the issue under investigation here rather than the extent. For those interested in the extent of disease, presumably the opposite of this might be true.

A potential pitfall of a meta analysis of diagnostic data could be the heterogeneity of patient characteristics (including disease stage) which would not necessarily be reflected in the test for heterogeneity which is only concerned with similarity or otherwise of outcomes.

The authors only searched Medline. This may well have picked up most relevant literature but neither the Cochrane Library nor Embase were used. Additionally, bibliographies in review and journal papers were hand-searched.

Updated evidence (2.1.1)

Summary

An update search identified four further papers on the topic of imaging to assess disease extent.

A systematic review (Shie *et al.* (2008) combined data from six cohort studies, four of which were prospective, to determine the efficacy of FDG-PET compared with bone scintigraphy (in the same patients) in identifying bone metastases from breast cancer. The authors found no clear difference between imaging modalities in identifying the metastases but determined that FDG-PET had a higher specificity despite having a smaller imaging field.

One small prospective non-randomised study (Schmidt *et al.*, 2008) compared whole body MRI and FDG-PET, given to the same individuals, in the detection of disease recurrence in patients with suspected clinical symptoms and/or raised tumour markers. The investigators found that the

imaging techniques were equally efficient at detecting organ metastases but that WB-MRI had a higher diagnostic accuracy and was also superior with respect to showing distant metastases, particularly in abdominal organs, brain and bone. Another larger prospective study (Ternier *et al.*, 2006) examined the efficacy of CT in detecting the presence of cancer recurrence in the breast and concluded that CT had a high diagnostic value in detecting local breast cancer recurrence but was unnecessary for routine use in most patients.

A small prospective comparative study (Bristow *et al.*, 2008) attempted to determine whether bone scans could be avoided if the pelvis was included in a CT scan of thorax and abdomen to detect bone metastases from breast cancer. They found that the CT scan had considerably better diagnostic accuracy and that use of the extended field might be economical if it obviated the necessity to use both modalities for screening.

References

Bristow AR (2008) Can computerised tomography replace bone scintigraphy in detecting bone metastases from breast cancer? A prospective study. *Breast* **17**: 98-103.

Schmidt GP., Baur-Melnyk A., Haug A., Heinemann V., Bauerfeind I., Reiser MF and Schoenberg SO (2008) Comprehensive imaging of tumor recurrence in breast cancer patients using whole-body MRI at 1.5 and 3 T compared to FDG-PET-CT. *Eur J Radiol* **65**: 47-58.

Shie P (2008) Meta-analysis: Comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer. *Clin Nucl Med* **33**: 97-101.

Ternier F., Houvenaeghel G., Lecrivain F., Brigand BL., Margain D., Brunelle S and Stefano DD (2006) Computed tomography in suspected local breast cancer recurrence. *Breast Cancer Research & Treatment* **100**: 247-254.

Evidence tables

Question: Imaging to assess the extent of disease
Created by: Karen Francis on 02/06/2007

Shie <i>et al.</i> (2008)
Design: Systematic review of cohort studies (diagnostic), evidence level: 1 Country: United States
Inclusion criteria: Included studies: Evaluated women of all ages with breast cancer at all stages regardless of treatment status Bone metastases were confirmed by CT, MRI or biopsy with a minimum follow-up of 6 months FDG-PET and scintigraphy were performed in the same subject not more than 3 months apart
Exclusion criteria: Excluded studies: In which only one scanning modality had been employed The numbers of true and false positives and negatives were omitted from the study report Sub-analysis data were not provided
Population: Number of patients = >184 age range: 28-83
Interventions: Women in the included studies had received both:

- 1] ^{18}F fluorodeoxyglucose used with PET scanning (FDG-PET) range: 2.8-11.8 mCi for up to 70 min and
- 2] 99m technetium hydroxymethylene diphosphonate (99m Tc-HDMP) scintigraphy range: 20-25 mCi with from 2 to 5 hours delay.

Two studies also employed single photon emission CT.

Outcomes:

To evaluate the diagnostic properties of FDG-PET and bone scintigraphy in their ability to detect osseous metastases in women with breast cancer.

Follow up:

Bone metastases were confirmed by CT, MRI or biopsy. Follow-up was no less than 6 months

Results:

1] FDG-PET:

Patient-based sensitivity = 81% (95%CI: 70-89)

Specificity = 93% (95%CI: 84-97)

Area under the curve (AUC) = 0.95

Lesion-based sensitivity = 69% (95%CI: 28-93)

Specificity = 98% (95%CI: 87-100)

AUC = 0.94

2] bone scan:

Patient-based sensitivity = 78% (95%CI: 67-86)

Specificity = 79% (95%CI: 40-95)

AUC = 0.78

Lesion-based sensitivity = 88% (95%CI: 82-92)

Specificity = 87% (95%CI: 29-99)

AUC = 0.91

General comments:

This paper describes the results of a small meta-analysis of six studies all of which compared FDG-PET and scintigraphy as a method to detect bone metastases in women with breast cancer. Women of all ages and of all cancer stages were included and there are no demographics given.

None of the included studies were RCTs – four were prospective cohort studies and two retrospective. The literature search had been thoroughly conducted by two researchers working independently. The search period covered the period January 1995 and November 2006. Data were also abstracted independently and disagreement was resolved by consensus. The analytical method employed to conduct the meta-analysis was appropriate and a summary receiver operating characteristic (ROC) curve was estimated in order to allow for variation of threshold between studies.

It was suggested that, for lesion-based data, FDG-PET performed less efficiently than scintigraphy because of the smaller imaging field i.e. from orbit to mid-thigh. Since treatment would be more likely to be based on the presence of metastatic disease rather than on the number of lesions, the results for patient-based data would be perhaps more relevant. Since two of the studies also employed SPECT, which can detect a greater number of spinal metastases, the results may be skewed in favour of scintigraphy in this meta-analysis.

The authors concluded that whilst there was no clear difference between imaging modalities FDG-PET, having a higher specificity, may be a better method both for detecting metastases and for assessing the response to therapy. The limitations of this review were due to the less than optimal quality of the included studies.

NB. Two papers included in this meta-analysis were previously appraised as part of the original evidence base (Abe *et al.*, 2005 and Nakai *et al.*, 2005).

Schmidt *et al.* (2008)

Design: Prospective case series (diagnostic) , evidence level: 3

Country: Germany

Inclusion criteria:

Women with a history of breast cancer presenting with some or all of the following: clinical symptoms, imaging results, pain, raised serum levels of tumour markers (CEA, CA, CA 15-3) which were suggestive of cancer recurrence.

Exclusion criteria:

Women who were in receipt of chemotherapy or radiotherapy prior to the study were excluded from the data analysis.

Population:

Number of patients = 33. Range: 24 to 79 years. Mean age: 55 years.

Interventions:

Whole body MRI (WB-MRI) was given on a 1.5T scanner (n = 23 patients) and images were obtained from head to mid-calves in coronal and sagittal orientations. Ten patients had imaging with a 3T scanner. Coronal T1w- TSE- and STIR-sequences, HASTE imaging of lungs, contrast-enhanced T1w- and T2w- TSE-sequences of the liver, brain and abdomen were performed.

Following a 6 hour fast, FDG-PET scanning was performed on a PET-CT scanner one hour after injection of 200 MBq of ¹⁸F-FDG. CT scans were performed at 40 mA/120 kV. Contrast-enhanced CT was also conducted at 60 mA/120 kV and images from different modalities were fused by means of computer software.

MRI images were reviewed by two radiologists and PET-CT scans by a radiologist and a nuclear medicine physicist. All reviewers worked independently and were blinded to other imaging results both prior and within the study.

Follow-up to confirm imaging results per patient included mammography (n = 3), breast ultrasound (n = 3), MRI (n =14), PET-CT (n = 12), bone scintigraphy (n = 10), radiographs (n = 9), WB-MRI (n = 6) and abdominal ultrasound (n = 5).

Outcomes:

To assess the diagnostic accuracy including sensitivity, specificity, negative and positive predictive values.

Concordance between imaging modalities.

Follow up:

-

Results:

The correlation between modalities in detecting lesions was 87%.

Lymph node:

PET/CT detected 21 lymph node metastases with sensitivity and specificity and accuracy of 96%

WB-MRI detected 16 lymph node metastases with sensitivity of 73%, specificity of 77% and accuracy of 75%.

Distant metastases:

PET/CT demonstrated a sensitivity of 91%, specificity of 86% and accuracy of 90%.

WB-MRI demonstrated a sensitivity of 95%, specificity of 92% and accuracy of 94%.

Bone:

WB-MRI allowed visualisation of 69 metastases in bone (vs 63 by PET/CT), 70 in the liver (vs 67) and both detected 15 metastases in the lung.

Additional metastases were found using WB-MRI (n = 2 in brain and n = 2 in bone).

FDG-PET/CT efficacy:

Sensitivity = 91% (170/186)

Specificity = 90% (69/77)

Accuracy = 91% (239/263)

WB-MRI efficacy:

Sensitivity = 93% (172/186)

Specificity = 86% (66/77)

Accuracy = 91% (238/263)

General comments:

The authors commented that although the imaging techniques are equally efficient at detecting organ metastases, WB-MRI had a higher diagnostic accuracy and was also superior in respect of showing distant metastases, particularly in abdominal organs, brain and bone.

The confirmatory tests were mainly image based as it was impracticable for the reviewers to obtain histological samples from multiple biopsies.

Despite being a comparative exercise, this was not a proper randomised trial and hence the grade of evidence is lower failing, as it does, to exclude numerous sources of bias.

Ternier *et al.* (2006)

Design: Prospective case series (diagnostic), evidence level: 3

Country: France

Inclusion criteria:

Women who had been conservatively treated for breast cancer and had been referred for breast CT as a result of suspicious imaging results and/or physical examination during follow-up.

Written informed consent was not required.

Exclusion criteria:

-

Population:

Number of patients = 103. Range: 32 to 82 years. Median age: 60 years.

Interventions:

Women with suspicious findings during routine follow-up were referred for physical examination, mammography of both breasts and a CT scan of the suspect breast (120 kV and 240 mA).

CT scans were assessed by two experienced radiologist who were blinded to the location of the primary breast cancer or the results of the physical examination or of conventional imaging. Disagreement was resolved by consensus. Malignancy was classified from all available information and lesions were subsequently surgically excised.

Outcomes:

To determine the sensitivity, specificity and accuracy of CT in detecting breast cancer recurrence

Follow up:

<p>Patients with benign lesions were followed up every 6 months for 2 years (mean = 47 months) during which time no incidences of recurrence were noted but some of these women later developed metastases (n=4), died from metastatic disease (n=2) or without cancer (n=1) and 5 patients were lost to follow-up. Of the 52 patients with local recurrence, at the time of publication 8 women had died and 1 was lost to follow-up.</p>
<p>Results: Of 103 patients investigated, 68 underwent surgery and 35 were followed up periodically. Of the 68 patients who underwent surgery, 52 were shown to have local breast cancer recurrence. Overall, there were apparently 52 malignancies and 51 benign lesions. 47/52 malignancies were detected by CT and 5 false -ve results were shown to be ductal carcinoma <i>in situ</i> (n=3) and 2 invasive carcinomas. There were also 5 false +ve results which were found to be due to cytosteatonecrosis (n=2), fibrosis, hyperplasia with atypia and lobular carcinoma <i>in situ</i>.</p> <p>CT efficacy: Sensitivity = 90% (47/52) Specificity = 90% (46/51) Accuracy = 90% (93/103)</p>
<p>General comments: This prospective study aimed to show the accuracy of CT in determining the presence of recurrent breast cancer. The authors were scrupulous in presenting the data and in following up the patients. They concluded that CT had a high diagnostic value in detecting local breast cancer recurrence but was unnecessary for routine use in most patients.</p>

<p>Bristow <i>et al.</i> (2008)</p>
<p>Design: Prospective comparative study (Diagnostic), evidence level 3. Country: UK</p>
<p>Inclusion criteria: None stated</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 77 (incl 1 male). Range: 35-90 years. Mean: 63 years.</p>
<p>Interventions: Consecutive patients presenting with suspected or confirmed MBC underwent CT of the thorax, abdomen and pelvis and bone scan. The two imaging modalities were given between four days and two weeks apart and were reviewed and discussed at MDT meetings. Diagnoses were made by consensus and additional information obtained, if necessary, from radiology and serum tumour markers.</p> <p>CT: multi-slice technique with oral and i.v. contrast. Images were reviewed by a team of radiologists who were blinded to the findings by bone scan.</p> <p>Bone scan: using i.v. Tc99m HDP at 500 MBq. Scans were reviewed independently by radiologists with a particular interest in nuclear medicine.</p>
<p>Outcomes: To determine whether bone scans could be avoided if the pelvis was included in a CT scan of thorax, abdomen to detect bone metastases from breast cancer.</p> <p>Sensitivity and specificity (calculated from published data).</p>
<p>Follow up:</p>

-

Results:

The following calculations were made from data within the paper:

CT scan:

Sensitivity = 97.5%

Specificity = 100%

Accuracy = 98.5%

Bone scan = 100%

Specificity = 67.5%

Accuracy = 85.5%

General comments:

This paper present the results of a small prospective but non-randomised comparative study matching CT scans of thorax, abdomen and pelvis with a full skeleton bone scan. The aim of the study was to determine whether, if the CT field was extended to include the proximal femur, any additional information gained on the number of bone metastases could obviate the necessity to use bone scans for this purpose.

The authors highlighted a potential saving to UK hospitals in imaging costs which might result by performing an extended CT scan rather than using both imaging methods to identify bone metastases as a routine staging procedure. They stated that metastases occurring outside the CT field of view were rare and that identifying extra bone metastases tended not to influence management of these patients.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

2.1.2 Monitoring the response to treatment

Short summary

The evidence for this topic was limited comprising six small case series, five of which were retrospective (Ciray *et al.*, 2001, Couturier *et al.*, 2006, Huber *et al.*, 2002, Stafford *et al.*, 2002, Mortimer *et al.*, 1996 and Linden *et al.*, 2006) and describing four different imaging methods. All patients had locally advanced or metastatic breast cancer which in most papers was stated to have been bone dominant disease.

MRI fat-suppressed-long-echo-time-inversion images were superior to T1-weighted-sequence images in accurately assessing the response to the treatment of bone metastases.

Radiography detected treatment responses to any form of cancer therapy within three months in 80% of cases and differentiated between regression and progression of disease.

Fluorodeoxyglucose-PET (FDG-PET) scans correlated positively with the levels of tumour markers and clinical category suggesting efficacy in the assessment of tumour response. Semi-quantitative analysis of scan data predicted overall survival and, after three cycles of treatment, correlated with the short term response to chemotherapy. Coupled to fluoroestradiol, PET scans accurately reflected the response to endocrine therapy.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Individuals with metastatic breast cancer requiring an assessment of the effect of treatment	<ul style="list-style-type: none"> • Plain radiographs (may not just be chest) • Liver ultrasound • CT • PET-CT • MRI • Bone scintigraphy 	Each with each other and in combination	<ul style="list-style-type: none"> • Ability to assess response to therapy • Ability to make treatment decisions

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

MRI

Ciray *et al.* (2001) conducted a very small retrospective study of MRI in the assessment of the response to treatment of breast metastases in bone. Patients received scans before and after chemotherapy and images were scored according to how well the images reflected the clinical response to therapy. The low patient number (n = 18) does not support a meaningful analysis of efficacy. This paper related the differences in image quality between T1-weighted sequences and recovery turbo spin-echo sequences, the latter of which were more accurate in this study.

Radiography

Huber *et al.* (2002) presented a larger (n = 274) retrospective study of the efficacy of radiography to determine the outcomes of the treatment of bone metastases by any therapy (included radiotherapy, chemotherapy, endocrine therapy or a combination). This is a completely observational study and does not test radiography against any gold standard but instead reports the findings over ten years of clinical follow-up. The authors claim that in 80% of patients radiography detected responses to any form of cancer treatment within three months and could differentiate between regression and progression

FDG-PET

Stafford *et al.* (2002) reported a small (n = 24) retrospective case series of patients in whom a response to chemotherapy or endocrine therapy for metastatic bone disease was assessed by FDG-PET imaging. The authors concluded that the uptake of FDG correlated positively with the levels of tumour markers and clinical category as determined by blinded reviewers. This would suggest that this imaging method could be useful in assessing treatment response but the size of the study does not offer much in the way of evidence.

FES-PET

Both Mortimer *et al.* (1996) and Linden *et al.* (2006) used FES-PET scanning as a means to determine the success of systemic therapy. The studies were both small in number (< 50) but had the same type of patient of approximately the same age. Patients received scans before and after endocrine therapy (or chemotherapy).

Mortimer *et al.* (1996) reported that FES imaging correlated with ER +ve status, determined subsequently by histology or immunochemical assay, in 67% of patients and with ER –ve status in 100% patients. The response rate for ER +ve patients treated with endocrine therapy was 56% and for ER –ve patients treated with chemotherapy was 80% and hence FES imaging might contribute to accurate determination of hormone status and hence to appropriate treatment. The patient numbers were not sufficient to draw firmer conclusions from this paper. There was an interesting suggestion, though, that negative FES uptake but positive receptor status might indicate a tumour that was functionally resistant to endocrine treatment.

Linden *et al.* (2006) compared the FES imaging results with the clinical response to treatment with endocrine therapy and found that those patients having more than one FES –ve site did not respond positively to systemic therapy whilst the majority of patients who demonstrated FES +ve sites showed either a positive response or stable disease.

References

Ciray I., Lindman H., Astrom KGO., Bergh J and Ahlstrom KH (2001) Early response of breast cancer bone metastases to chemotherapy evaluated with MR imaging. *Acta Radiol* **42**: 198-206.

Huber S., Ulsperger E., Gomar C., Koderhold G and Czembirek H (2002) Osseous metastases in breast cancer: Radiographic monitoring of therapeutic response. *Anticancer Res* **22**: 1279-1288.

Linden HM., Stekhova SA., Link JM., Gralow JR., Livingston RB., Ellis GK., Petra PH., Peterson LM., Schubert EK., Dunnwald LK., Krohn KA and Mankoff DA (2006) Quantitative fluoroestradiol positron emission tomography imaging predicts response to endocrine treatment in breast cancer. *J Clin Oncol* **24**: 2793-2799.

Mortimer JE., Dehdashti F., Siegel BA., Katzenellenbogen JA., Fracasso P and Welch MJ (1996) Positron emission tomography with 2-[F-18]fluoro-2-deoxy-D-glucose and 16 alpha-[F-18]fluoro-17 beta-estradiol in breast cancer: Correlation with estrogen receptor status and response to systemic therapy. *Clin Cancer Res* **2**: 933-939.

Stafford SE., Gralow JR., Schubert EK., Rinn KJ., Dunnwald LK., Livingston RB and Mankoff DA (2002) Use of serial FDG PET to measure the response of bone-dominant breast cancer to therapy. *Acad Radiol* **9**: 913-921.

Evidence tables

Question: Imaging to assess the response to treatment
Created by: Karen Francis on 22/01/2007

Mortimer <i>et al.</i> (1996)
Design: Prospective case series (diagnosis, screening), evidence level: 3 Country: United States
Inclusion criteria: All women with locally advanced or metastatic breast cancer. Written informed consent.
Exclusion criteria: None stated.
Population: Number of patients = 43, age range 33 to 76 years, median age = 56 years.
Interventions: Prior to systemic therapy, patients underwent PET scanning. Images were obtained 90 min after

iv injection of radiolabeled glucose (FDG) or estradiol (FES) analogues The same area was scanned using the other radiolabel (within a 3 day period for 81% of patients - maximum interval between scans was 9 days).

FDG: 370MBq after 4hrs fasting

FES: 222MBq

Outcomes:

To evaluate the potential role of FES-PET and FDG-PET in predicting the efficacy of systemic therapy.

FDG and FES images were prospectively evaluated, independent of one another, by at least 2 nuclear medicine physicians, at least one of whom was blinded to clinical and correlative radiographic findings.

FDG images were graded as 'definitely abnormal', 'probably abnormal', 'equivocal' or 'normal'.

FES images were graded according to presence or absence of areas of increased uptake as '+ve' or '-ve'. There was 100% agreement between the blinded and unblinded reviewers.

Follow up:

After imaging, patients received systemic therapy at the discretion of the therapist and all clinical follow-up was provided by that same physician.

Clinical follow-up of patients was for a median of 23 months. Patients were assessed for treatment outcome and Kaplan Meier survival analysis was presented.

Results:

Patients were determined to have locally advanced or inflammatory breast cancer (n = 25), widespread metastatic disease (n = 15) or recurrent disease of the chest wall (n = 3).

Tumours assessed by histology or immunochemical assay were ER +ve in 21 patients, ER -ve in 20 patients and undeterminable in 2 patients because of technical difficulties. FES imaging correlated with ER +ve status in 16/21 (76%) patients and with ER -ve status in 20/20 patients (100%). In 2 patients with ER status unknown, one was classified FES +ve.

FDG-PET uptake did not correlate with FES status nor was FDG-PET uptake correlated with ER or menopausal status (data not shown).

50 foci were studied in 17 patients with metastatic disease. FES-PET results concurred with 92% of these lesions (in 13 patients (76%)) with respect to ER status.

Survival data:

ER +ve/FES +ve (n = 16): 3CR + 6PR. ORR = 9/16 (56%)

ER +ve/FES -ve (n = 5): 2CR + 1PR. ORR = 3/5 (60%)

ER -ve/FES -ve (n = 20): 7CR + 9PR. ORR = 16/20 (80%)

ER nk/FES +ve (n = 1): 0CR + 1PR. ORR = 1/1 (100%)

ER nk/FES -ve (n = 1): 0CR + 0PR. ORR = 0/1 (0%)

General comments:

This paper describes a study of women with breast cancer (inflammatory, locally advanced, recurrent and metastatic) who underwent two PET scans after being given iv FDG or FES. Cancer staging was determined by histology, physical evaluation, complete blood count, liver function studies and chest radiography. Tumour samples were also assessed histologically and a quantitative measurement was made of ER protein. It was hoped to correlate FES uptake with ER protein levels.

The authors hypothesised that those patients with ER +ve histology but who are FES -ve might be functionally resistant to endocrine therapy (meaning that the presence of ER did not

necessarily indicate binding of estrogen to the tissues).

The results of FDG scanning were not reported but were used in the assessment of patient staging along with other tests.

Ciray *et al.* (2001)

Design: Retrospective case series (diagnosis, screening), evidence level: 3

Country: Sweden

Inclusion criteria:

Patients with newly diagnosed or recently progressed bone metastases secondary to BC, confirmed by histology of CT-guided biopsy.

Informed consent

Exclusion criteria:

None stated

Population:

Number of patients = 18, age range 38 to 68 years, mean age = 53 years.

Interventions:

Patients received a minimum of 3 course of either standard FEC (5-fluorouracil, epirubicin and cyclophosphamide)(n = 7), tailored (higher dose) FEC with G-CSF (n = 5), epirubicin and docetaxel with G-CSF (n = 5) or paclitaxel (n = 1)

Patients received MRI scans 0-35 days (median 8 days) before therapy and 80-160 days (median 124 days) afterwards.

Outcomes:

T1-weighted sequences (T1) and fat-suppressed long echo time inversions recovery turbo spin-echo sequences (TE) were assessed in their ability to measure the response to therapy of a single chosen metastasis.

The reference standard was a combination of clinical evaluation, bone scintigraphy and radiography. These investigations were carried out in parallel with MRI both before and after chemotherapy.

Definitions of tumour response for each reference standard and for the MRI sequences were very fully detailed in the paper. Responses in all cases were graded as 'complete response', 'partial response', 'no change' and 'progressive disease'.

Follow up:

-

Results:

There were no complete responses assessed by the reference standard.

T1 images:

'Partial response' (n = 12) identified in 2 images. 7 images were incorrectly scored 'no change' and 3 'progressive disease'

'No change' (n = 4) identified in all images

Progressive disease (n = 2) identified in both images.

TE images:

'Partial response' (n = 12) identified in 7 images. 5 images were incorrectly scored 'no change'

'No change' (n = 4) identified in all images

Progressive disease (n = 2) identified in both images.

General comments:

This paper describes a small retrospective study where 18 patients from a single centre in Sweden were studied between October 1995 and April 1999.

6/11 patients with newly diagnosed metastases and 2/7 patients with recently progressed metastases had received adjuvant chemotherapy > 6 months before the study.

MR images were assessed by one reviewer who was blinded to the reference standard evaluation. Any uncertainty was overcome by obtaining a second opinion. The two MR sequence images were reviewed separately and then compared with the reference standard.

Given the very low patient numbers, analysis of efficacy is not warranted. 8/18 response were correctly identified by T1 and 13/18 by TE.

Huber *et al.* (2002)

Design: Retrospective case series (diagnosis, screening), evidence level: 3

Country: Austria

Inclusion criteria:

Demonstrable bone metastases from radiography or bone scintigraphy

Patients must have had one baseline radiograph and a second follow-up within 3 months

Exclusion criteria:

None stated

Population:

Number of patients = 274, age range 23 to 84 years, mean age = 53 years.

Interventions:

One principle metastasis was followed in each patient, selected on image quality of a series of radiographs, clarity of metastatic destruction and location. This principal lesion was analysed for each patient in relation to treatment modality used (RT, chemotherapy, endocrine therapy or combination). Signs of regression or progression were chosen for evaluation.

Patients had a mean of 20.8 radiographs each

Outcomes:

Determination of reliable (and presumably reproducible) radiographic signs indicative of positive or negative treatment effects such that future treatment decisions could be based on this imaging technique.

Follow up:

Mean follow-up of 29.1 months (range: 3-81 months) and period of observation of the group was 10 years

Results:

In 274 patients, 117 (42.7%) had osteolytic lesions, 79 (28.8%) had osteosclerotic lesions and 78 (28.4%) had mixed lesions.

111 patients showed a positive response to therapy:

Sclerosis of osteolytic or mixed lesions = 32

Marginal sclerosis = 37

Stable = 29

Reduction osteosclerotic density = 7

Reduction in size = 5

Disappearance of lesion = 1

163 patients showed progression:
Increase in size or number of osteoclastic metastases = 40
Increase in size or number of osteolytic metastases = 91
Increase in size or number of mixed metastases = 25
Lysis in sclerotic or mixed lesions = 7

General comments:

This paper describes a mainly anecdotal study of the strength of radiography in the detection of disease progression or otherwise of bone metastases. The findings are not verified by any other means.

The authors contend that this imaging can successfully determine a positive response to therapy (of whichever kind) and differentiate between regression and progression of disease. They also state that such a response was evident in 88/111 of the positive responders on the first follow-up, at an average time period of 2.9 months from therapy initiation.

Stafford *et al.* (2002)

Design: Retrospective case series (diagnosis, screening), evidence level: 3

Country: United States

Inclusion criteria:

Breast cancer with bone dominant metastatic disease confirmed by biopsy, or conventional imaging (bone scanning, MRI, CT or plain radiography)
Clear uptake with FDG-PET scan in order to provide a basis for comparison with follow-up
At least 2 FDG-PET scans > 1 and < 18months apart
Written informed consent

Exclusion criteria:

Patients with proven metastases but negative FDG-PET scan

Population:

Number of patients = 24, age range 31 to 72 years, mean age = 45 years.

Interventions:

18 FDG-PET: After 4hr fasting, patients were given 260-270MBq of 18 FDG and then scanned after 45 - 60min.

Outcomes:

To evaluate the feasibility of FDG-PET imaging to provide an effective and quantitative means of evaluating bone metastasis response to therapy (including cytotoxic chemotherapy and endocrine therapy).

Uptake was expressed as units of maximum standard uptake value (SUV). One lesion was chosen as the index lesion which was used for evaluating the change in FDG uptake over serial scans.

Clinical response to therapy was compared with changes in SUV of the index lesion.

Follow up:

Sufficient to determine the response to treatment.

Results:

There was always positive concordance between the change in SUV of the index lesion and the change in FDG uptake overall and this in turn always matched the change in serum tumour markers ($P < 0.001$) and the clinical category of response determined by the blinded reviewers ($P < 0.004$).

A full table of individual data is presented showing each patient, their treatment interval, time between scans, type of treatment, response, tumour marker (CA 27.29) level and percentage change in SUV. No summary data are included other than the above.

General comments:

This paper presents a retrospective case series of patients who underwent FDG-PET imaging in a single US institution between May 1996 and December 2000.

FDG-PET scans were evaluated by nuclear medicine physicians with experience in PET imaging who were blinded to the clinical outcome.

Information gathered to determine clinical response included serial measures of blood tumour markers, conventional images and subjective symptom changes. Two medical oncologists who were blinded to patient identity and FDG-PET results categorised the treatment response (disease progression, stable disease, disease regression).

Statistical comparison of variables such as SUV, tumour markers and clinical outcome was quantified by Pearson or Kendall (a distribution-free test of independence and a measure of the strength of dependence between two variables) rank correlation tests.

Authors conclude that FDG-PET might be a useful tool for measuring the response of bone metastases to therapy but the patient number is very low for this conclusion to be sound.

Linden *et al.* (2006)

Design: Retrospective case series (diagnosis, screening), evidence level: 3

Country: United States

Inclusion criteria:

Recurrent or metastatic breast disease

ER positive tumour status

Previous FES-PET at the time of endocrine therapy with ≥ 6 months follow-up

At least 1 site of measurable disease of ≥ 1.5 cm

Discontinuation of any tamoxifen therapy at least 2 months before FES-PET

Exclusion criteria:

Liver metastases

Population:

Number of patients = 47, age range 35 to 76 years, mean age = 56 years.

Interventions:

(¹⁸F) Fluoroestradiol positron emission tomography (FES-PET) either before or just after the commencement of endocrine therapy (usually aromatase inhibitors).

Outcomes:

Qualitative and quantitative analyses of a relationship between FES-PET and the clinical response to treatment with endocrine therapy.

Qualitative: Efficacy was scored as either +ve (if all sites of known disease were apparent by FES-PET) or -ve (if one or more sites of disease were imaged by FDG-PET and other imaging modalities but not FES-PET).

Quantitative: Imaging was used to estimate the rate of FES uptake and clearance from areas of interest (identified by FDG-PET). (Greater uptake would indicate a correspondingly higher level of ER receptors and therefore presumably a better response to endocrine therapy). Data were dichotomised according to threshold calculations and efficacy was scored by ROC analysis.

Follow up:

At least 6 months after FES-PET imaging.

Results:

Treatment response (77% agreement between reviewers)

Complete response (CR) = 0 (0%)

Partial response (PR) = 11 (23%)

Stable disease (SD) = 18 (38%)

Progressive disease (PD) = 18 (38%)

Qualitative results:

6/47 (13%) patients had 1 or more FES -ve sites. Of these, none had a response to treatment (CR or PR), 2 (33%) had SD and 4 (66%) had PD.

41/47 patients demonstrated FES uptake at all sites of disease. Of these, 11 (41%) had a response to treatment, 16 (39%) had SD and 14 (34%) had PD.

The trend for the ability of qualitative FES-PET to predict the response to endocrine treatment was not significant ($P = 0.014$).

Quantitative FES results:

15/47 patients had FES uptake values lower than the computed threshold (i.e. < 1.5). None of these patients showed a response to endocrine therapy. Of the 32 patients with FES uptake levels > 1.5 , eleven showed a positive treatment response and 21 had no response or stable disease ($P < 0.01$)

14/37 patients had FES clearance rates (flux) lower than the computed threshold (0.02 ml per min per g). None of these patients showed a response to endocrine therapy. Of the 24 patients with FES flux > 0.02 ml per min per g, 10 showed a positive treatment response and 14 had no response or stable disease ($P < 0.005$). 10 patients were not assessable for FES flux.

General comments:

This paper describes a retrospective analysis of patients who had received FES-PET imaging before, or just after starting, endocrine therapy for ER +ve MBC.

The authors investigated the relationship between FES uptake (hence ER expression) and response to endocrine therapy. Regions of interest were identified by conventional imaging techniques including FDG-PET, CT, bone scans and MRI.

Treatment response was analysed by 3 medical oncologists, blinded to FES imaging results. Qualitative analysis was performed retrospectively by one experienced observer, blinded to subsequent treatment outcome.

The authors conclude that ER functional in vivo analysis is a reliable method of assessing the likely response to endocrine therapy. Qualitative results were non-significant, possibly due to low patient number.

Updated evidence (2.1.2)

Summary

Only one small case series (Couturier *et al.*, 2006) was found to update the evidence on imaging to assess the response to treatment.

The researchers of this work hoped to show that PET scanning, undertaken after one and three cycles of chemotherapy, could predict the short term response to treatment (measured at six

months) and the longer term overall and event-free survival. They found that semi-quantitative analysis of standardised uptake values, which showed successive decreases with therapy after three cycles, correlated significantly with the clinical response and could predict overall survival.

Reference

Couturier O., Jerusalem G., N'Guyen JM and Hustinx R (2006) Sequential positron emission tomography using [F-18] fluorodeoxyglucose for monitoring response to chemotherapy in metastatic breast cancer. *Clin Cancer Res* **12**: 6437-6443.

Evidence tables

Question: Imaging to assess the response to treatment
Created by: Karen Francis on 02/06/2007

Couturier <i>et al.</i> (2006)
Design: Prospective case series (prognostic) Country: Belgium
Inclusion criteria: Women with confirmed MBC Hormone refractory or hormone receptor –ve Suitable candidates for chemotherapy
Exclusion criteria: Women with symptomatic brain metastases
Population: Number of patients = 20. Range: 25 to 67 years. Median age = 55 years
Interventions: Study participants were in receipt of chemotherapy, either anthracyclines (n = 4) or, for those who had been pre-treated with anthracyclines in the adjuvant setting, taxane-based therapy (docetaxel n = 12, paclitaxel n = 4). All treatments were given on a three-weekly basis. Response to treatment was monitored by blood analysis (tumour markers) and conventional imaging. In addition, after a fasting period of at least 4 hours participants were given 0.5 MBq 18F and PET scans were performed 69 ± 13 minutes thereafter. These studies were performed at baseline, at day 21 after the first cycle and 21 days after the third cycle.
Outcomes: To evaluate whether PET scanning undertaken after one and three cycles of chemotherapy could predict the short term response to treatment measured at 6 months and the long term objective response to chemotherapy: overall survival (OS) and event-free survival (EFS).
Follow up: All participants were followed through to their death.
Results: PET scan and the visual response to therapy: After one cycle of chemotherapy, 12 women showed a partial response and, of these, 9 responded to treatment at 6 months. Eight women, after one cycle, showed stable or progressive disease and two eventually responded to treatment. After 3 cycles of chemotherapy, 16 women showed a response but six did not respond to treatment and 3/4 women who were classified as stable later failed to respond to therapy. This assessment after one or three cycles did not therefore correlate strongly (75% success) with the eventual response to chemotherapy. PET scan and average standardised uptake value (SUV):

SUV changes after one cycle of chemotherapy did not predict the clinical response regardless of calculation method. After three cycles, however, there was a marked difference in SUV values between treatment responders (52-56% decrease from 1st to 3rd scan) compared with non-responders (16-26% decrease from 1st to 3rd scan). These differences were significant for all SUV calculation methods. The statistical analyses presented showed that metabolic responses after three cycles were predictive of clinical response after six cycles. (P = 0.02).

Clinical response measured at 6 months predicted the OS (P = 0.005) but not EFS. Metabolic response measured as changes in SUV after the third cycle of chemotherapy also predicted the OS (P = 0.0012) but not EFS

General comments:

This paper presented the result of a small observational study which aimed to investigate if FDG-PET scanning could predict the response to chemotherapy in women treated for MBC. Whilst a response was not apparent on visual assessment of PET scans after three cycles, the semi-quantitative analysis of SUV and their successive decreases with therapy after three cycles correlated significantly with the clinical response which would occur after six cycles.

Both the clinical response, measured by conventional methods, and the metabolic response, measured as changes in SUV after the third cycle of chemotherapy, predicted the OS with significance but neither could predict EFS.

Whilst well conducted and reported this is a small observational study without study controls which limits its strength as evidence.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

2.2 Reassessment of endocrine and Her2 status on disease progression

Short summary

The evidence for this topic was provided by seventeen observational studies all of which compared paired (from the same patient) biopsy or fine needle aspirate samples from primary and locoregional or metastatic tumour tissue. Her2 (Niehans *et al.*, 1993, Shimizu *et al.*, 2000, Gancberg *et al.*, 2002, Carlsson *et al.*, 2004, Regitnig *et al.*, 2004, Gong *et al.*, 2005, Zidan *et al.*, 2005, Lorincz *et al.*, 2006, Rom *et al.*, 2006, Pectasides *et al.*, 2006, Tapia *et al.*, 2007 and Santinelli *et al.*, 2008) and/or endocrine receptor (Spataro *et al.*, 1992, Johnston *et al.*, 1995, Lower *et al.*, 2005, Rom *et al.*, 2006, Shimizu *et al.*, 2000 and Brankovic-Magic *et al.*, 2002) status was determined by immunohistochemistry or *in situ* hybridisation. All study participants had advanced breast cancer.

The majority of papers were concerned with identifying the rate of status change but did not address overall survival, time to progression or quality of life. Approximately 15% of patients showed a change in endocrine receptor status, from positive to negative, comparing primary with locoregional or metastatic tumour samples. 93% of patients tested for Her2 status showed no change between paired samples.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with ER/PR and HER2 status known in primary tumour	Reassessment of status on biopsy from recurrence	Each with each other	<ul style="list-style-type: none"> Changes in receptor expression between the two samples Time to progression Improved survival Better quality of life

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

All but one study gave sufficient data to allow determination of the proportion of patients who had positive receptor status both for primary and recurrent and/or metastatic tumour biopsies. Broadly similar, the studies used three main methods to derive this data, most commonly immunohistochemistry (IHC) and fluorescent *in situ* hybridisation (FISH) and, less commonly, radioimmunoassay (RIA). Specific differences, for examples, staining methodology, antisera etc. may have had some influence on the overall results but, generally, Her2 receptor overexpression was more likely to be lost in samples from distant metastases but maintained in those from local recurrent disease. Endocrine status usually declined in recurrent and metastatic disease, often as a response to hormone treatment.

Table 2.2.1 presents details of all but one of the studies showing the percentage of samples with Her2 +ve or endocrine +ve status in first and second biopsies. The method of status determination is also shown for comparison. Wirk and Geiger (2006 - meeting abstract only) did not report absolute numbers of Her2, ER or Pr +ve samples but gave the numbers of results that were in accord overall between paired samples (31/39).

Study	Type	No of ppts.	% +ve primary	% +ve mets	P	Methodology and regions from which second samples obtained
Carlsson <i>et al.</i> , 2004	Her2	47	55	55	nsd	IHC (HerceptT) FISH (PathVysion) and CISH - lymph nodes
Niehans <i>et al.</i> , 1993	Her2	14	36	36	nsd	IHC (Triton) - lung, liver, lymph nodes, skin, CNS, adrenal, ovary, breast, kidney, spleen, bowel, omentum, heart
Gong <i>et al.</i> , 2005	Her2	60	33	30	nsd	FISH (Vysis) - lymph nodes, soft tissue, lung, liver, bone, pleura
Shimizu <i>et al.</i> , 2000	Her2	21	38	38	nsd	IHC (Nichirei) - 'local', liver, lung, lymph nodes
Rom <i>et al.</i> , 2006	Her2	70	36	34	nsd	IHC (Dako) - 'local recurrent disease'

Lorincz <i>et al.</i> , 2006	Her2	23	17	9	Not tested	IHC (HercepT) FISH (INFORM Ventana) - bone
Gancberg <i>et al.</i> , 2002	Her2	107	13	19	0.03	IHC (HercepT) FISH (Vysis) - bone, soft tissue, liver, lung, brain, other
Regitnig <i>et al.</i> , 2004	Her2	31	14	35	0.001	IHC (HercepT) FISH (PathVysion) - lymph nodes, bone, skin, ipsi. breast, lung, liver, pancreas, stomach, kidney, peritoneum
Zidan <i>et al.</i> , 2005	Her2	58	24	34	0.07	IHC (Dako) FISH (no details) - bone, skin, soft tissue, liver, lungs, pleura
Pectasides <i>et al.</i> , 2006	Her2	16	100	65	0.014	IHC (HercepT) CISH (Zymed) - skin, breast, lymph nodes, palate, ovary, liver
Spataro <i>et al.</i> , 1992	ER	401	65	58	Not tested	Ligand binding assay - 'local', soft tissue, bone, viscera, contralateral breast
Lower <i>et al.</i> , 2005	ER	200	58	49	$\kappa=0.4$	IHC (no methodology given) - 'local', lymph nodes, bone, lung, brain, liver, orbit, ovary, skin, colon, pancreas
Rom <i>et al.</i> , 2006	ER	70	49	22	<0.01	IHC (Dako) - 'local recurrent disease'
Study	Type	No of ppts.	% +ve primary	% +ve mets	P	Methodology and regions from which second samples obtained
Johnston <i>et al.</i> , 1995	ER	72	51	29	<0.0001	IHC (Dako) - 'local recurrence', lymph nodes, skin
Shimizu <i>et al.</i> , 2000	ER	21	50	25	0.19	Immunoassay - 'local', liver, lung, lymph nodes
Lower <i>et al.</i> , 2005	PR	200	54	25	$\kappa=0.24$	IHC (no methodology given) - 'local', lymph nodes, bone, lung, brain, liver, orbit, ovary, skin, colon, pancreas
Rom <i>et al.</i> , 2006	PR	70	32	28	<0.01	IHC (Dako) - 'local recurrent disease'
Shimizu <i>et al.</i> , 2000	PR	21	57	30	0.11	Immunoassay - 'local', liver, lung, lymph nodes
Johnston <i>et al.</i> , 1995	PR	72	42	19	0.001	IHC (Dako) - 'local recurrence', lymph nodes, skin
Brankovic-Magic <i>et al.</i> , 2002	ER/PR	23	57	39	Not tested	Immunoassay - lymph nodes, skin, pleura

Table 2.2.1 Comparison of the percentages of endocrine and Her2 +ve samples from primary and recurrent or metastatic tumours from the same patients.

Her2 status

Ten full studies (Carlsson *et al.*, 2004, Gancberg *et al.*, 2002, Gong *et al.*, 2005, Shimizu *et al.*, 2000, Lorincz *et al.*, 2006, Niehans *et al.*, 1993, Regitnig *et al.*, 2004, Rom *et al.*, 2006, Zidan *et al.*, 2005 and Pectasides *et al.*, 2006) examined the issue of whether or not patients with known Her2 status on diagnosis of their primary breast cancer carried the same status in cells of either recurrent or distant metastases. All papers were of equivalent quality and most studies were well conducted and reported but suffered the limitation of small sample number and the obvious retrospective nature of the tissue sampling. The evidence, therefore, is not generally of a high standard.

In five of these studies (Carlsson *et al.*, 2004, Gong *et al.*, 2005, Shimizu *et al.*, 2000, Niehans *et al.*, 1993 and Rom *et al.*, 2006) Her2 +ve status was not statistically significantly altered between first and second samples. The majority of the 'second' samples appear to have been taken from areas of locoregional disease (lymph nodes, skin, soft tissue and breast) rather than from distant metastases. It should be noted that Niehans *et al.* (1993) used material from autopsy samples – prolonged tissue fixation might have adversely affected Her2 IHC staining and the results may therefore be unreliable.

In four studies (Gancberg *et al.*, 2002, Regitnig *et al.*, 2004, Zidan *et al.*, 2005 and Pectasides *et al.*, 2006) the data show a statistically significant change in the levels of Her2 overexpression between first and second samples and in all but one case (Pectasides *et al.*, 2006) this change was an increase from primary to mainly distant metastases. The percentage of patients across these three studies that developed Her2 +ve metastatic tumours from a Her2 –ve primary was approximately 10% (n = 196).

Pectasides *et al.* (2006) showed a highly significant decrease in Her2 receptor overexpression in the locoregional and metastatic second samples although the patient number (n=16) is rather too low to make the statistical conclusions of much evidential value. All these patients had been treated with trastuzumab.

The paper by Lorincz *et al.* (2006) does not state the statistical significance of a reported decline in Her2 overexpression from 17% to 9% between seventeen paired samples, the second of which were all of bone metastases. It may be helpful to question the suitability of bone as material for IHC since immunogenicity might be lost in the decalcification step – perhaps explaining the dramatic loss of Her2 receptor staining in metastatic samples.

It has been suggested that locoregional tumours might be more likely to have the same Her2 status as the original primary tumour but that distant metastases might represent a clonal outgrowth bearing genetic mutations not detected in the primary and therefore express a different level of Her2 oncogene transcript and/or receptor protein. Another view is that, if tumours are heterogeneous for certain markers including Her2, their status may change in response to a treatment which targets part of the cell population but allows the unaffected cells to flourish and produce a tumour with a different marker status.

These small studies are different from one another in many respects e.g. histological methodology, primary antisera, nature of tissue etc making them inadequate to provide strong evidence for this question. The majority of authors either did not express a view on routine testing of recurrent or metastatic tumours or did not believe that this was practical or warranted. The few that did express this view (n = 4) thought that re-testing might be relevant for patients that had a primary tumour recently and reliably tested as Her2 –ve on the basis that the knowledge of Her2 conversion might affect treatment decisions and survival outcomes.

Endocrine status

Six full papers (Spataro *et al.*, 1992, Lower *et al.*, 2005, Rom *et al.*, 2006, Johnston *et al.*, 1995, Brankovic-Magic *et al.*, 2002 and Shimizu *et al.*, 2000) addressed the question of whether or not endocrine (estrogen and/or progesterone) receptor (ER/PR) status changed between primary and recurrent or metastatic tumours.

In all but two papers (Spataro *et al.*, 1992 and Brankovic-Magic *et al.*, 2002) in which data were not tested statistically, the authors had reported significant reductions in ER and PR in both locoregional and distant metastases compared with the primary tumours. The study showing highest significance was Johnston *et al.* (1995) in which all 72 patients had received treatment with tamoxifen and had *de novo* or acquired resistance.

The patient number in these studies was higher than for the question regarding Her2 status (n = 787) but, unfortunately, the largest of these studies (Spataro *et al.*, 1992) did not present statistical analyses of the observed loss in ER expression which occurred in 7% of the 401 patients.

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Evidence tables

Question: Changes in receptor expression from primary tumour to recurrence
 Created by: Karen Francis on 01/02/2007

Carlsson <i>et al.</i> (2004)
Design: Prospective case series (other), evidence level: 3 Country: Sweden
Inclusion criteria: Patients with metastatic breast cancer that had provided tissue samples of both primary tumour and lymph node metastasis. The presence of distant metastases (samples not taken).
Exclusion criteria: Histological samples of poor quality
Population: Number of patients = 47
Interventions: Paired biopsy samples from primary and lymph node metastases were processed for determination of Her2 protein and gene expression. Her2 protein overexpression was determined by means of IHC on paraffin embedded samples. The primary antiserum was rabbit anti-human c-erbB-2 oncoprotein (Dako). Both negative and positive controls were used. Her2 protein expression was scored by HercepTest criteria based on a 0 to 3+ scale. Both 2+ and 3+ were considered as 'positive' and confirmed as FISH/CISH +ve. Her2 gene amplification was determined by chromogenic (CISH) and/or fluorescent (FISH) <i>in situ</i> hybridisation (Pathvysion dual probe) which were in 100% accord with one another.
Outcomes: Quantitative analysis of the degree of Her2 overexpression was carried out on each paired set of samples to assess any differences in expression between primary and recurrent or metastatic tumours Survival data not reported.
Follow up: N/A
Results:

<p>Histological grade of tumour (n = 47): Grade I (least aggressive) = 11% Grade II (intermediate) = 64% Grade III (most aggressive) = 25%</p> <p>T-stage (n = 47): T1 (< 2cm) = 21% T2 (2-5cm) = 53% T3 (> 5cm) = 23% T4 (extensive) = 2%</p> <p>Concordance between primary and metastatic samples: Primary 0 (n = 13) - lymph node 0 (n = 13) Primary 1+ (n = 8) - lymph node 1+ (n = 2) and 0 (n = 6) Primary 2+ (n = 3) - lymph node 2+ (n = 3) Primary 3+ (n = 23) - lymph node 3+ (n = 22) and 2+ (n = 1)</p> <p>The percentage of overexpression of Her2 protein was 26/47 (55%) in both primary and metastatic tumours.</p> <p>6 metastatic tumours were downgraded from 1+ to 0 (which are both considered 'negative' anyway) and 1 metastatic tumour was downgraded from 3+ to 2+ (both of which were considered as 'positive'). Therefore there were no conversions from positive to negative or vice versa.</p> <p>General comments: This paper presents a small case series of patients in which samples of both primary and lymph node metastatic tumour had been obtained and analysed.</p> <p>Paired samples were coded and analysed separately by reviewers blinded to the pairing.</p> <p>Patient characteristics were not given but 94% patients were post-menopausal and 100% presumed to be female.</p> <p>It is not clear how many of the IHC samples had corresponding FISH or CISH analysis - in the abstract this was stated to have been done in 'some patients'.</p>

Gancberg <i>et al.</i> (2002)
Design: Retrospective case series (other), evidence level: 3 Country: Switzerland
Inclusion criteria: Samples from breast cancer patients had to include both primary tumour and at least one distant metastasis (not locoregional)
Exclusion criteria: None stated.
Population: Number of patients = 107.
Interventions: Paired biopsy samples from primary and (first detected chronologically) distant metastatic tumours tissues were processed for determination of Her2 protein and gene expression.
Her2 protein overexpression was determined by means of IHC on paraffin embedded samples using the HercepTest (Dako). Both negative and positive controls were used.

Her2 protein expression was scored by HercepTest criteria based on a 0 to 3+ scale. 3+ was considered as 'positive'

Her2 gene amplification was determined by fluorescent *in situ* hybridisation (FISH) using a Vysis triple probe.

Outcomes:

Quantitative analysis of the degree of Her2 overexpression was carried out on each paired set of samples to assess any differences in expression between primary and metastatic tumours.

Survival data not presented.

Follow up:

N/A

Results:

Due to technical difficulties, only 100 paired samples scored by IHC were available for comparison:

Concordance between primary and metastatic samples (IHC):

Primary: 0 (n = 57) metastasis: (n = 52)

Primary: 1+ (n = 14) metastasis: (n = 21)

Primary: 2+ (n = 16) metastasis: (n = 8)

Primary: 3+ (n = 13) metastasis: (n = 19)

There were 6 changes from -ve to +ve status and no changes from +ve to -ve.

The percentage of patients with overexpression of Her2 protein was 13/100 (13% with 95% CI: 6% - 20%) in primary and 19/100 (19% with 95% CI: 11% - 27%) in metastatic tumours (P = 0.03).

Data for samples analysed by FISH were available for only 68 paired primary and metastatic tumours:

Concordance between primary and metastatic samples (FISH):

Primary: amplification (n = 16) metastasis: (n = 17)

Primary: no amplification (n = 52) metastasis: (n = 51)

The percentage of patients with Her2 gene amplification was 16/68 (24%) in primary and 17/68 (25%) in metastatic tumours.

There was discordance in 5 samples, three of which were FISH +ve in the metastatic lesion but not in the primary and conversely two that were FISH +ve in the primary but not in the metastatic lesion.

The number of patients assessed as being Her2 +ve from their primary tumours was statistically higher when tested by FISH than by IHC (P = 0.04) but there was no significant difference in the assessment of Her2 status between the two methods in metastatic samples (P = 0.73).

General comments:

This paper presents a retrospective case series of patients in which samples of both primary and metastatic tumour had been obtained and analysed. Patients had initially been tested from 1981 to 1999.

FISH analysis was impossible (due to technical difficulties) in some cases and hence the IHC scores were confirmed in only 68/107 originally available paired samples (64%).

Scoring of IHC data was classified by one reviewer who was blinded to the FISH data and the Her2 status of the patient. Similarly, FISH data were classified by two reviewers who were blinded with regard to Her2 status and IHC data. In two cases there was discord until the FISH was repeated, at which point the reviewers were in agreement about the result.

Analysis of Her2 status between primary and metastasis samples was performed with the first chronological metastasis only since it was considered by the authors that multiple sampling from individual patients would possibly skew the results - this is most probably true.

Appropriate statistical analyses were performed such that the information obtained about the Her2 scoring by studying one metastasis could be generalised for the metastatic disease as a whole (since 17 patients had multiple metastases). However, this same stringency was not applied to the subset of 68 paired samples for FISH analysis.

Gong *et al.* (2005)

Design: Retrospective case series (other), evidence level: 3
Country: Canada (federal state, Commonwealth Realm)

Inclusion criteria:

Patients with known Her2 status for their primary and paired metastatic tumours.

Exclusion criteria:

None stated.

Population:

Number of patients = 60, age range 26 to 79 years, mean age = 52 years.

Interventions:

Paired biopsy or fine needle aspirate samples from primary and metastatic (locoregional n = 43 and distant n = 17) tumours were processed for determination of Her2 gene expression.

Gene expression was measured by fluorescent *in situ* hybridisation (FISH) using the PathVysion probe kit (Vysis).

Outcomes:

Quantitative analysis of the degree of Her2 gene expression was carried out on each paired set of samples to assess any differences in expression between primary and recurrent or metastatic tumours.

Survival data not reported.

Follow up:

N/A

Results:

Nuclear grade of tumour (n = 58):
 Grade 1 = 3%
 Grade 2 = 29%
 Grade 3 = 65%

T-stage (n = 31):
 T1 (< 2cm) = 33%
 T2 + (> 2cm) = 18%

Concordance between primary and metastatic samples:

Primary: +ve (n = 20) metastasis: (n = 18)
 Primary: -ve (n = 40) metastatic: (n = 42) (nsd).

<p>General comments: This paper describes a retrospective case series of patients from whom samples from primary and metastatic or recurrent tumours were reviewed and compared. Samples were collected between 1996 and 2003.</p> <p>32/60 patients had received chemotherapy before their metastases had been samples.</p> <p>The authors measured Her2 gene (but not protein) expression because they were of the opinion that technical issues with IHC may explain the occasionally reported disparity in Her2 status between primary and recurrent tumours.</p> <p>Appropriate statistical analysis was carried out on the results.</p> <p>In 2 patients the Her2 gene was highly over-amplified in the primary but not metastatic samples. Reasons given were that one patient had three foci in one breast, only one of which was sampled. The other patient had polysomic CEP17 in a liver metastasis which, distorting the Her2/CEP17 ratio, gave a false negative result.</p> <p>Additionally, samples taken after chemotherapy did not show a change in Her2 status measured by gene expression in that subgroup (n = 32) of patients.</p>
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Lorincz <i>et al.</i> (2006)
<p>Design: Retrospective case series (other), evidence level: 3 Country: Hungary</p>
<p>Inclusion criteria: None stated</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 48, median age = 59 years.</p>
<p>Interventions: Paired biopsy samples from (archived) primary and metastatic bone metastases were processed for determination of Her2 protein and gene expression.</p> <p>Her2 protein overexpression was determined by means of IHC on paraffin embedded samples using the HercepTest (Dako)</p> <p>Her2 protein expression was scored by HercepTest criteria based on a 0 to 3+ scale. Both 2+ and 3+ were considered as 'positive'.</p> <p>Her2 gene amplification was determined by fluorescent <i>in situ</i> hybridisation (FISH) (Oncor INFORM system, Ventana). FISH was performed on samples that were scored 2+ or 3+ by IHC or on samples from patients whose results differed between primary and metastases.</p>
<p>Outcomes: Quantitative analysis of the degree of Her2 overexpression was carried out on each paired set of samples to assess any differences in expression between primary and recurrent or metastatic tumours.</p> <p>Survival data were not recorded.</p>
<p>Follow up:</p>

N/A
<p>Results: Paired samples were only available in 23 patients.</p> <p>Primary tumour grade: Grade I: 1/23 Grade II: 10/23 Grade III: 12/23</p> <p>Concordance between primary and metastatic samples: Primary 0 or 1+ (n = 20) - metastases 0 or 1+ (n = 21) Primary 2+ (n = 1) - metastases 2+ (n = 0) Primary 3+ (n = 2) - metastases 3+ (n = 2) All primary samples were FISH +ve but only 2 metastatic samples.</p> <p>There was discordance in 2 samples, both of which were Her2 +ve in the primary tumour (either by IHC or FISH) but Her2 –ve in the metastases.</p>
<p>General comments: This paper describes a retrospective study on patients who had received surgery for primary and metastatic breast cancer at two centres. All the metastases were in bone.</p> <p>The FISH system is different from the more commonly used Vysion system in that absolute gene copy number is assessed rather than by the calculation of a ratio of Her2 gene transcript and CEP 17 satellite DNA.</p> <p>Concordance between IHC and FISH was not total. 1/4 Her2 IHC 2+ samples and 4/5 Her2 IHC 3+ samples were in agreement.</p>

Lower <i>et al.</i> (2005)
<p>Design: Retrospective case series (other), evidence level: 3 Country: United States</p>
<p>Inclusion criteria: None stated</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 200, age range 27 to 84 years.</p>
<p>Interventions: Pathological reports or patient charts were accessed for the determination of estrogen receptor (ER) and progesterone receptor (PR) status in paired samples from primary and metastatic samples. There are no details of the methodology used in the original testing except a reference to dextran charcoal method (probably radioimmunoassay).</p> <p>In cases where status information was not available, archived histological specimens were processed by means of immunoassay using "standard techniques".</p>
<p>Outcomes: To investigate the concordance of primary and recurrent or metastatic ER and PR content. A third of tumours were local recurrence.</p>
<p>Follow up:</p>

N/A
<p>Results: 200 patients had paired results for ER and, of these, 174 also had paired results for PR.</p> <p>Tumour stage at diagnosis (n = 200): Stage 1: 28 ER -ve, 30 ER +ve = 58 Stage 2: 36 ER -ve, 64 ER +ve = 100 Stage 3: 15 ER -ve, 12 ER +ve = 27 Stage 4: 5 ER -ve, 7 ER +ve = 12 Unknown: 1 ER -ve, 2 ER +ve = 3</p> <p>Concordance between primary and metastatic samples (ER = 200) Primary: +ve (n = 115) metastasis: (n = 97) Primary: -ve (n = 85) metastasis: (n = 103)</p> <p>Concordance between primary and metastatic samples (PR = 173) Primary: +ve (n = 93) metastasis: (n = 43) Primary: -ve (n = 80) metastasis: (n = 130)</p> <p>Effect of hormonal status of primary / metastatic or recurrent tumour on survival (median OS): ER +ve / ER +ve = 1131 days ER +ve / ER -ve = 669 days ER -ve / ER +ve = 1111 days ER -ve / ER -ve = 580 days +ve / -ve differs from +ve / +ve (P <0.05)</p> <p>PR +ve / PR +ve = 1030 days PR +ve / PR -ve = 776 days PR -ve / PR +ve = 1077 days PR -ve / PR -ve = 639 days -ve / -ve differs from +ve / +ve (P <0.001) and -ve / +ve (P < 0.02)</p>
<p>General comments: This paper described a moderately sized retrospective study which looked at the influence of hormone status, in primary and recurrent or metastatic disease, on clinical outcome.</p> <p>Authors conclude that the apparently high level of discordance between primary and metastatic samples for ER and PR status reinforces the need to obtain fresh biopsy material at recurrence/metastases.</p> <p>The other point is that it appears to be the hormone status of the metastatic tumour, rather than the primary that is significantly correlated with clinical outcome.</p>
Rom <i>et al.</i> (2006)
<p>Design: Retrospective case series (other), evidence level: 3 Country: Germany</p>
<p>Inclusion criteria: Patients with invasive breast cancer of all stages (with or without nodal involvement) and locoregional recurrence Prior treatment with lumpectomy or modified mastectomy.</p>
<p>Exclusion criteria: Women with clinical evidence of distant metastases</p>

Second primaries in another quadrant.
<p>Population: Number of patients = 70, age range 26 to 85 years, median age = 49 years.</p>
<p>Interventions: Paired samples from primary and recurrent tumour samples were processed for determination of Her2 protein by IHC on formalin fixed and paraffin embedded tissues. The primary antiserum was rabbit anti-c-erbB-2 polyclonal antibody (Dako).</p> <p>Her2 protein expression was scored by HercepTest criteria based on a 0 to 3+ scale. Samples judged to be 2+ had confirmation of Her2 status by FISH. These and IHC 3+ samples were considered +ve.</p> <p>IHC was also used to measure the expression of endocrine receptors on formalin fixed and paraffin embedded tissues using anti-ER (ID5) and anti-PR (PgR636) clones (Dako) respectively.</p>
<p>Outcomes: Quantitative analysis of the degree of Her2 protein overexpression was carried out on each paired set of samples to assess any changes between primary and recurrent or metastatic tumours. In addition the expression of estrogen and progesterone receptors was likewise compared in paired samples.</p> <p>There were no survival data.</p>
<p>Follow up: N/A</p>
<p>Results: T-stage (n = 70): T1 (< 2cm) = 29% T2 + (> 2cm) = 71%</p> <p>Nuclear grade (n = 70): Grade 1: 2.9% Grade 2: 35.7% Grade 3: 61%</p> <p>Concordance between primary and metastatic samples (Her2 n = 67): Primary: +ve (n = 24) metastasis: (n = 23) Primary: -ve (n = 43) metastasis: (n = 44) (nsd) 3 recurrent tumours had converted from +ve to -ve and 2 had converted from -ve to +ve.</p> <p>Concordance between primary and metastatic samples (ER n = 69): Primary: +ve (n = 34) metastasis: (n = 15) Primary: -ve (n = 35) metastasis: (n = 54) (P < 0.01) 64.7% recurrent tumours had converted from +ve to -ve and 4.3% had converted from -ve to +ve.</p> <p>Concordance between primary and metastatic samples (PR n = 69): Primary: +ve (n = 22) metastasis: (n = 19) Primary: -ve (n = 19) metastasis: (n = 50) (P < 0.01) 50% recurrent tumours had converted from +ve to -ve and 11.6% converted from -ve to +ve.</p>
<p>General comments: This paper describes a retrospective case series of patients for whom tumour samples of primary and recurrent breast cancer were available for review. Treatment or biopsy had occurred between 1996 and 2001.</p>

Authors conclude that, in the case of endocrine receptors, the high percentage of status changes, particularly from positive to negative, would have an obvious impact on treatment options. However the Her2 status seems to remain stable.

Shimizu *et al.* (2000)

Design: Retrospective case series (other), evidence level: 3

Country: Japan

Inclusion criteria:

None stated

Exclusion criteria:

None stated

Population:

Number of patients = 21, age range 35 to 75 years, mean age = 50 years.

Interventions:

Paired samples from primary and metastatic tumour tissues were processed for determination of Her2 protein by IHC (n = 17) and immunoassay (n = 4).

Her2 protein overexpression was determined by means of IHC on paraffin embedded samples. The primary antiserum was rabbit anti-c-erbB-2 polyclonal antibody (Nicherei).

Her2 protein expression was scored by criteria set by Tsuda et al 1990 - based on the intensity of staining of the cell membrane as being either strong (and hence positive) or weak with cytoplasmic staining (negative).

Her2 protein was measured in four patients by standard sandwich enzyme immunoassay, using the same antisera as that used for IHC. Her2 status was deemed positive at above 18 ng per ml of protein.

Immunoassay was used to measure the expression of both PR and ER. Values above 10 fmol per mg of protein (ER) and 13 fmol per mg of protein (PR) were graded as positive.

Outcomes:

Quantitative analysis of the degree of Her2 overexpression was carried out on each paired set of samples to assess any changes between primary and recurrent or metastatic tumours.

Follow up:

N/A

Results:

Histological grade of tumour (n=21):

Grade I (least aggressive) = 9.5%

Grade II (intermediate) = 19%

Grade III (most aggressive) = 71.5%

T-stage (n=21):

T1 (< 2cm) = 14%

T2 (2-5cm) = 62%

T3 (> 5cm) = 14%

T4 (extensive) = 10%

Concordance between primary and metastatic samples (Her2):

Primary: +ve (n = 8) metastasis: (n = 8)

<p>Primary: –ve (n = 13) metastasis: (n = 13) (nsd)</p> <p>Concordance between primary and metastatic samples (ER n=20): Primary: +ve (n = 10) metastasis: (n = 5) Primary: –ve (n = 10) metastasis: (n = 15) (P = 0.19 = nsd)</p> <p>Concordance between primary and metastatic samples (PR n=20): Primary: +ve (n = 12) metastasis: (n = 6) Primary: –ve (n = 8) metastasis: (n = 14) (P = 0.11 nsd)</p> <p>General comments: This paper describes a small retrospective case series of patients who had had both primary and asynchronous metastatic lesions removed and analysed for expression of Her2, PR and ER. Patients had undergone surgery between April 1996 and September 1998.</p> <p>Her2 status appears not to have changes between primary and metastatic lesion (mostly locoregional) and the hormones receptors show a non-significant reduction with disease progression.</p> <p>Interestingly, of the 8 patients showing changes to either ER and/or PR status, 3 had received hormone therapy as adjuvant therapy but 5 patients had received no adjuvant therapy.</p> <p>Although a reasonable study, the low patient numbers reduce the statistical strength.</p>
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<p>Spataro <i>et al.</i> (1992)</p>
<p>Design: Retrospective case series (other), evidence level: 3 Country: Switzerland</p>
<p>Inclusion criteria: Patients were untreated before the first sample was obtained for estrogen assay.</p>
<p>Exclusion criteria: None stated.</p>
<p>Population: Number of patients = 401, age range 19 to 81 years, median age = 53 years.</p>
<p>Interventions: Ligand binding assays were used to quantify estrogen receptors (ER) on biopsy samples from primary and recurrent breast cancer tumours.</p> <p>Assays were performed at several laboratories, all of which participated in the International (Ludwig) Breast Cancer Study Group Trials. Inter-laboratory concordance was confirmed.</p>
<p>Outcomes: Paired samples were assayed for ER and data were compared to determine the frequency of status change between initial disease and recurrence.</p> <p>Endocrine status was +ve when ER < 10fmol per µg cytosol protein and –ve when ER ≥ 10fmol per µg cytosol protein.</p> <p>Data were further stratified into groups in order to study the prognostic significance to overall survival (OS) of the rate of concordance between 1st and 2nd ER assays, treatment given and time elapsed between assays.</p>
<p>Follow up: Median follow-up from diagnosis was 6yrs (range: 2 - 12yrs).</p>

Results:

At the time of initial diagnosis, 274 patients had operable whilst 127 had locally advanced disease.

Tumour stage in operable patients (n = 274):

T1 (< 2cm) = 72
T2+ (> 2cm) = 120
unknown = 82

After a median interval of 27 months (range: 2 - 122 months) a second ER assay was performed. At this point patients had local or contralateral breast relapse as the only site of disease (n = 267), regional or distant soft tissue involvement (n = 68) or bony disease/visceral involvement (n = 66).

Concordance between primary and metastatic samples (ER n = 401):

Primary: +ve (n = 261) metastasis +ve: (n = 231)
Primary: -ve (n = 140) metastasis -ve: (n = 170)

There was a conversion from ER -ve to ER +ve in 76 patients and a conversion from ER +ve to ER -ve of 46 patients and therefore a net gain/loss of 30 patients in each group.

The number of patients whose status changed from ER +ve to ER -ve was significantly higher in those in whom disease relapse occurred < 1yr (P = 0.0004) or > 3yrs (P = 0.0003).

For the 274 treatable patients, the conversion from ER +ve to ER -ve occurred more often in those who received some therapy than those who did not but conversion from ER -ve to ER +ve was lower in patients receiving treatment (no statistics).

Patients receiving endocrine therapy had higher conversion rate of ER +ve to ER -ve than those patients who did not receive endocrine therapy (P = 0.02).

Conversion from ER -ve to ER +ve occurred with equal frequency in all treatment groups.

There was no prognostic significance to OS in patients that had a status change from ER +ve to ER -ve For patients who were initially ER -ve conversion to ER +ve within 1yr had no prognostic significance but if conversion occurred later than 1yr then such patients had a better OS than patients who had remained ER -ve throughout (P = 0.006).

General comments:

This paper describes a large cohort of breast cancer patients who were treated at one of five centres internationally. Data were retrospectively reviewed from those patients whose primary and recurrent tumours were both assayed for estrogen receptor. Assays had been performed between 1978 and 1991

This is a very thorough paper on a fair number of patients. The statistics are appropriate to the problem. There may be variation between laboratories in their determination of ER status although this is unlikely to have affected what appear to be statistically strong outcomes to the point of losing significance.

Zidan *et al.* (2005)

Design: Retrospective case series (other), evidence level: 3

Country: Israel

Inclusion criteria:

Patients treated for both primary and metastatic tumours from which biopsy samples were

available.
Exclusion criteria: Ipsilateral metastatic axillary lymph nodes
Population: Number of patients = 58, age range 29 to 82 years, median age = 56 years.
Interventions: Paired biopsy samples from primary and metastatic tumours were processed for determination of Her2 protein and gene expression. Her2 protein overexpression was determined by means of IHC on paraffin embedded samples. The primary antiserum was mouse monoclonal clone CB11 (Dako). Her2 protein expression was scored by HercepTest criteria based on a 0 to 3+ scale. Both 2+ and 3+ were considered as 'positive' and confirmed if FISH +ve. Her2 gene amplification was determined by fluorescent <i>in situ</i> hybridisation (FISH) of which no methodological details were given. It was stated that all samples tested by IHC and FISH gave a concordant positive result.
Outcomes: Quantitative analysis of the degree of Her2 overexpression was carried out on each paired set of samples to assess any differences in expression between primary and recurrent or metastatic tumours.
Follow up: N/A
Results: Concordance between primary and metastatic samples: Primary 0 or 1+ (n = 44) - metastases 0 or 1+ (n = 38) Primary 2+ (n = 2) - metastases 2+ (n = 2) Primary 3+ (n = 12) - metastases 3+ (n = 18) There was discordance in 8 samples, one of which was Her2 +ve in the primary tumour but Her2 -ve in the metastases and conversely seven that were Her2 -ve in the primary tumour but Her2 +ve in the metastatic lesion. Of the 7 patients who converted to Her2 +ve status, 3 had died without receiving trastuzumab. Four patients that were treated with trastuzumab had variously: a partial response for 9 months, minimal or no response (n = 2) or complete remission for 13+ months.
General comments: This paper describes a retrospective case series of patients treated at a single centre from which samples had been taken from primary and metastatic tumours. These were processed to determine and compare Her2 status.

Wirk and Geiger (2006)
Design: Retrospective case series (other), evidence level: 3- Country: United States
Inclusion criteria: None stated
Exclusion criteria: None stated

<p>Population: Number of patients = 39.</p>
<p>Interventions: Paired samples from primary and recurrent tumour samples were processed for determination of Her2 protein by IHC on formalin fixed and paraffin embedded tissues. The primary antiserum was rabbit anti-c-erbB-2 polyclonal antibody (HercepTest).</p> <p>Her2 protein expression was scored by HercepTest criteria based on a 0 to 3+ scale. Samples were also processed for FISH analysis (Pathvysion) to determine Her2 gene expression.</p> <p>IHC was also used to measure the expression of endocrine receptors but no details were given.</p>
<p>Outcomes: Quantitative analysis of the degree of Her2 and endocrine overexpression was carried out on each paired set of samples to assess any changes between primary and recurrent or metastatic (n = 1) tumours.</p> <p>No survival data were presented.</p>
<p>Follow up: N/A</p>
<p>Results: 39/160 patients had available data on Her2 status at the primary breast cancer stage together with biopsy data on recurrent, asynchronous lesions.</p> <p>Number of Her2 status results in accord between primary and recurrent lesion = 31 Number of IHC 2+ to IHC 0 = 4 (-ve to -ve) Number of IHC 3+ to IHC 1+ = 1 (+ve to -ve) Number of IHC 0 to IHC 3+ = 2 (-ve to +ve) Number of FISH+ to FISH1 = 1 (+ve to -ve)</p> <p>Number of ER and PR status results in accord between primary and recurrent lesion = presumed 31 Number ER +ve or PR +ve to ER -ve / PR -ve = 7 Number of ER -ve / PR -ve to ER +ve / PR +ve = 2 Number of ER +ve / PR +ve to ER +ve / PR -ve = 4 Number of ER -ve / PR -ve to ER -ve / PR +ve = 1</p> <p>3/8 patients with change of Her2 status also had change of endocrine status.</p>
<p>General comments: A retrospective case series was described of the comparison of medical records for 160 patients that had provided samples for primary and recurrent breast cancer. Patient records between 1997 and 2003 were reviewed.</p> <p>Of the 160 patients records reviewed only 39 patients had received a re-examination of their Her2 status on disease recurrence.</p> <p>The authors regarded the change of IHC 2+ to 0 as a status change but the immunohistochemical test was not confirmed by FISH analysis in these samples and hence might not be reliable.</p> <p>This was a meeting abstract only and hence the data were very limited but was included for completeness. The full study is, apparently, 'forthcoming'.</p>

Brankovic-Magic <i>et al.</i> (2002)
Design: Retrospective case series (other), evidence level: 3 Country: Serbia
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 23, age range = 32-77 years, median age = 47 years
Interventions: Paired biopsy samples were processed, from either a cytosolic fraction of frozen tumour tissue or of pleural effusion, for a five point dextran-coated charcoal (DCC) assay of ER and PR. Values above 10 fmol per mg of protein (ER) and 20 fmol per mg of protein (PR) were graded as positive. For the classification of endocrine status, ER +ve / PR +ve and ER -ve / PR +ve samples were considered 'positive' whilst ER -ve / PR -ve and ER +ve/PR -ve were considered 'negative'. Receptor status was determined simultaneously in 4/23 sample pairs.
Outcomes: To determine the usefulness of steroid receptor content in breast cancer metastases for therapeutic planning Progression-free interval (PFI) Treatment response: complete response (CR), partial response (PR) and stable disease (SD).
Follow up: Patients were followed up for a median of 10 months (range: 2-12 months).
Results: Tumour stage at diagnosis (n = 23): T1 (< 2cm) = 11 T2 (2-5cm) = 9 T3 (> 5 cm) = 4 T4 (extensive) = 1 Unknown = 1 Steroid status of primary tumours (n = 23): ER -ve / PR +ve = 13 ER +ve / PR +ve = 0 ER +ve / PR -ve = 10 ER -ve / PR -ve = 0 Steroid status of metastatic tumours (n = 23): ER -ve / PR +ve = 9 ER +ve / PR +ve = 0 ER +ve / PR -ve = 14 ER -ve / PR -ve = 0 Concordance between primary and metastatic samples: ER = 12/23 (52%) PR = 9/23 (39%) ER and PR = 6/23 (26%) Concordance of endocrine status between primary and metastatic samples:

Primary: +ve (n = 13) metastasis: (n = 9)
 Primary: -ve (n = 10) metastasis: (n = 14)

There was no statistically significant difference in PFI between patients with positive (n = 13) or negative (n = 10) steroid status in the primary tumour but there was a significant difference in PFI between patients with positive (n = 9) and negative (n = 14) steroid status in the metastases (P <0.02).

Treatment response (n = 23):
 CR = 8
 PR = 6
 SD = 1

Conversion of PR status occurred in treatment responders (n = 9/15) and non-responders (5/8). For the latter group, the switch was only from +ve to -ve but for responders was both +ve to -ve (n = 4) and -ve to +ve (n = 5).

General comments:

This paper describes a small case series of breast cancer patients from which paired tissue samples had been obtained at the time of disease diagnosis and on detection of metastatic disease. Metastatic samples were taken from the lymph nodes (n = 11), skin (n = 4) or as pleural effusion (n = 8).

13/19 patients had not been treated between successive steroid receptor samplings and 6/19 had received chemotherapy.

Receptor status and treatment outcome was analysed with respect to PR only.

From the lack of data on PFI and the Kaplan-Meier analysis it appears that, at the time of writing, follow-up had not been sufficiently long to have recorded a median PFI. It is not possible to determine how PFI was correlated with receptor status as above. Because of this uncertainty it may be unsafe to make assumptions that endocrine status and PFI are related. In addition, the patient number is too low for such analysis.

Regitnig *et al.* (2004)

Design: Retrospective case series (other), evidence level: 3

Country: Austria

Inclusion criteria:

None stated

Exclusion criteria:

None stated

Population:

Number of patients = 31, age range 33-78, median age = 54

Interventions:

Formalin fixed, paraffin embedded tissue samples had been processed for IHC. Her2 protein expression was measured by the HercepTest (Dako) and scored accordingly from 0 to 3+. Results were confirmed by the use of a tissue microarray using the same test kit.

Her2 expression was assessed using fluorescent *in situ* hybridisation (FISH) using the PathVysion kit (Vysis) with combined Her2 and chromosome 17 probes. This method was not successful on metastatic bone material due to DNA breakdown.

<p>Outcomes: To determine if Her2 amplification and protein overexpression occur <i>de novo</i> in breast metastases in late stage disease.</p>
<p>Follow up: N/A</p>
<p>Results: Concordance between primary and metastatic samples (IHC): Primary: 0 or 1+ (n = 25) - metastases: 0 or 1+ (n = 17) Primary: 2+ (n = 3) - metastases: 2+ (n = 8) Primary: 3+ (n = 3) - metastases: 3+ (n = 6) There were 8 changes from –ve to +ve status and no changes from +ve to –ve (P0.001). FISH confirmed these results. 24/28 primary tumours were negative for Her2 gene amplification and 4/28 were positive. In 18 metastatic tumours evaluable by FISH, 7 showed gene amplification. In 4 cases FISH amplification was seen in the metastases but not in the primary tumour.</p>
<p>General comments: This paper describes a retrospective study of deceased breast cancer patients, the case files of which were examined, samples retrieved and data recorded. All had histology results for paired tissue samples taken from primary and metastatic tumours. Files covered the period 1984 to 2001. Patient ages relate to the time of their surgery not this study. None of the patients in the study had received trastuzumab. Metastases in these patients were sampled from bone (n = 8), skin (n = 6), brain (n = 5), liver (n = 3) and other visceral sites.</p>

<p>Niehans <i>et al.</i> (1993)</p>
<p>Design: Retrospective case series (other), evidence level: 3 Country: USA</p>
<p>Inclusion criteria: None stated</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 30</p>
<p>Interventions: Formalin fixed, paraffin embedded archival tumour samples were processed for IHC using monoclonal anti-Her2 antibody TAB-250 (Triton). Positive and negative staining controls were used.</p>
<p>Outcomes: To determine the rate at which tumours acquire the ability to overexpress Her2 protein during progression from primary lesions to metastatic sites at the end of the disease course. Her2 protein expression was scored from 0-4+ where 3+ and 4+ were defined as strongly positive, 1+ and 2+ weakly positive and only 0 was scored as 'negative' for the purposes of comparison.</p>

<p>Follow up: N/A</p>
<p>Results: Only 13 patients had histology for both primary and metastatic tissue.</p> <p>Concordance between primary and metastatic tumours: Primary 0: (n = 8) - metastases: (n = 6) Primary 1+: (n = 1) - metastases (n = 3) Primary 2+: (n = 0) - metastases (n = 0) Primary 3+: (n = 2) - metastases (n = 0) 1 patient had three 4+ and one 3+ metastases Primary 4+: (n = 3) - metastases (n = 5) There were no conversions from Her2 +ve to -ve or vice versa.</p>
<p>General comments: This paper details a retrospective case series of patients who, having died of metastatic breast cancer, had their case reports reviewed alongside histological samples which were processed for Her2 IHC by the authors.</p> <p>Samples of metastatic tissue (from 2-5 per patient) were taken from lungs (n = 23), liver (n = 21), lymph node (n = 11), skin (n = 8), CNS (n = 6), contralateral breast (n = 3) and viscera (n = 20).</p> <p>The Her2 scoring in this study differs from the Hercept definitions and may classify more samples as 'positive' (either weakly or strongly) and only a complete lack of staining was deemed 'negative'.</p> <p>Samples from the primary tumour were only available in 14/30 patients. This lack of data makes the patient number rather low for evidential purposes.</p>

<p>Johnston <i>et al.</i>(1995)</p>
<p>Design: Retrospective case series (other), evidence level: 3 Country: United Kingdom</p>
<p>Inclusion criteria: Patients had received tamoxifen, either as adjuvant therapy or as primary medical therapy after diagnosis and had either progressed or relapsed on this treatment.</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 72.</p>
<p>Interventions: Patient charts were accessed for the determination of estrogen receptor (ER) and progesterone receptor (PR) status in paired samples.</p> <p>From patients that had received tamoxifen as primary treatment, samples were taken from the same tumour before and after therapy. From patients that had received adjuvant tamoxifen, samples were taken from the excised primary tumour and from the recurrent (or metastatic) tumour.</p> <p>ER expression was determined by IHC on formalin fixed and paraffin wax embedded tissues. The primary antiserum was mouse monoclonal anti-human ER (clone ID5 Dako).</p> <p>PR expression was also was determined by IHC on formalin fixed and paraffin wax embedded</p>

tissues. The primary antiserum was mouse monoclonal anti-human PR (Abbott).

Negative and positive staining controls were used.

Outcomes:

To determine if a change of ER expression occurs in patients that develop tamoxifen resistance and could be used to predict treatment response.

Staining intensity in cells within a field of view was scored 0 - 3 and this score multiplied by the percentage of cells at this intensity to give an overall score. This was repeated for 10 fields and the mean score was used for comparative purposes.

Follow up:

N/A

Results:

Patients with acquired tamoxifen resistance (n = 18):

Primary tumour ER +ve = 16

Relapsed tumour ER +ve = 11 (4 of which showed increased immunoreactivity) (mean score P < 0.0001).

5 tumours had converted from ER +ve to ER -ve with tamoxifen treatment. The 2 ER -ve primary tumours remained ER -ve.

Patients with de novo tamoxifen resistance (n = 20):

Primary tumour ER +ve = 3

Non-primary tumour ER +ve = 0 (mean score P = 0.008)

Patients on adjuvant tamoxifen who relapsed (n = 34):

Primary tumour ER +ve: 18

Non-primary tumour ER +ve = 10 (mean score P = 0.0002) Of the 18 primaries, 12 recurred on tamoxifen with locoregional disease and 6 with metastatic disease.

Patients with acquired tamoxifen resistance (n = 18):

Primary tumour PR +ve = 11

Relapsed tumour PR +ve = 10 (mean score nsd)

Patients with de novo tamoxifen resistance (n = 20):

Primary tumour PR +ve = 6

Non-primary tumour PR +ve = 0 (mean score nsd)

Patients on adjuvant tamoxifen who relapsed (n = 34):

Primary tumour PR +ve: 13

Non-primary tumour PR +ve = 4 (mean score P = 0.001).

General comments:

This paper describes a study of breast cancer patients in which samples of primary and recurrent tumours were compared for endocrine receptor status.

At the time of writing IHC was not routinely used as a means of testing endocrine status after tamoxifen treatment due to the possibility of generating false negative results. To validate IHC, duplicate samples were processed for both IHC and for an immunoassay known not to be affected by tamoxifen. The two methods showed a concordance rate of 96%.

Of the 72 patients, 38 had been given tamoxifen as first treatment for primary breast cancer. Of these 38 patients, 18 suffered a relapse (acquired tamoxifen resistance) and 20 did not respond (de novo tamoxifen resistance). A further 34 patients had received adjuvant tamoxifen after surgery but had suffered a relapse - in 15 patients the relapse was at the same site as the

original tumour and in 19 patients at a different site (lymph node or skin). Histological samples were therefore paired from the same tumour or from the primary and a metastatic site.

Pectasides *et al.* (2006)

Design: Retrospective case series (other), evidence level: 3

Country: Greece

Inclusion criteria:

Patients with MBC who developed metastases accessible for biopsy or fine needle aspiration (in patients with poor performance status).

Patients were being treated with trastuzumab at the time of recurrence.

Initial tumour samples with Her2 status of IHC 3+ or IHC 2+ with CISH +ve test.

Exclusion criteria:

None stated.

Population:

Number of patients = 16.

Interventions:

Paired primary and metastatic samples had Her2 status determined by IHC (HercepTest) and (CISH) using a digoxigenin-labelled Her2/neu probe (Zymed).

Her2 protein expression was graded 0-3+ and compared between paired samples. The slides were reviewed by an independent pathologist.

CISH was graded according to the number of red (positive) signals per tumour cell. 1-5 gene copies per nucleus in > 50% cells was defined as -ve. 6-10 gene copies in > 50% cells was defined as low level amplification and > 10 gene copies as clear amplification.

Outcomes:

To determine if Her2 status differs between primary and metastatic tumours.

Median time to progression (TTP).

Follow up:

N/A

Results:

Initial Her2 status was measured in primary tumour in 12/16 patients and metastatic tumour in 4/16 patients. 15 patients had an IHC 3+ score and 1 patient had IHC 2+ / CISH +ve score.

10/16 patients had conserved Her2 status. All had an initial biopsy from breast and second biopsies from chest wall (n = 4), liver (n = 1), breast (n = 1), lymph node (n = 2), soft palate (n = 1) or ovary (n = 1).

6/16 patients had altered Her2 status from 3+ to either 0 or 1+ (-ve) by IHC or from CISH +ve to -ve. Initial biopsies had been taken from breast (n = 2), chest wall (n = 2), skin (n = 1) or lymph node (n = 1). Second biopsies were taken from skin (same patient), chest wall (n = 4) or breast (formerly lymph node).

The change in status was statistically significant (P = 0.014).

Median TTP overall = 11 months (range: 4-36 months)

Median TTP for patients with status change = 9.5 months (range: 2-14 months)

Median TTP for patients with conserved status = 12 months (range: 7-36 months) P < 0.001

General comments:

This paper describes a very small case series in which Her2 status was studied in primary and metastatic tumour samples. The low patient number makes the statistical analysis of little value.

The numbers of chemotherapeutic regimes received by patients, the median time of chemotherapy and trastuzumab treatment administered between the two biopsies were found to be of no significant difference between patients who had conserved or altered Her2 status.

Updated evidence (2.2)

Summary

Two moderate sized retrospective studies of equivalent quality were found to update the evidence on endocrine status discordance between primary to metastatic or recurrent disease tissue. Both papers related to Her2.

Tapia *et al.* (2007) presented data from paired biopsy samples of primary and distant metastatic tissue from the same individuals. Her2 status was determined by fluorescent *in situ* hybridisation (FISH). Unexplained discordance between samples occurred in 3 cases (2.9% of the total study population). All other apparent discrepancies were explained on the basis of interpretational differences rather than as a result of biological conversion.

Santinelli *et al.* (2008) performed a similar study but with different conclusions. Her2 status was determined by immunohistochemistry and FISH. Examination by two blinded reviewers revealed that, compared with the primary tissue, recurrent or metastatic tissue was discordant with respect to Her2 status in 21% of cases. The authors focused on the varied biological bases for disparity and concluded by recommending testing of Her2 in patients with metastatic breast cancer.

References

Santinelli A., Pisa E., Stramazotti D and Fabris G (2008) HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. *Int J Cancer* **122**: 999-1004.

Tapia C., Savic S., Wagner U., Schonegg R., Novotny H., Grilli B., Herzog M., Barascud AD., Zlobec I., Cathomas G., Terracciano L., Feichter G and Bubendorf L (2007) HER2 gene status in primary breast cancers and matched distant metastases. *Breast Cancer Research* **9** (3).

Evidence tables

Question: Changes in receptor expression from primary tumour to recurrence
 Created by: Karen Francis on 04/06/2007

Tapia <i>et al.</i> (2007)
Design: Retrospective case series, evidence level 3 Country: Switzerland
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 105, age range 26 to 85 years, mean age = 58 years
Interventions: Paired biopsy samples from a primary cancer and from distant metastases in each patient were processed for determination of Her2 gene expression by fluorescent <i>in situ</i> hybridisation (FISH).

Additional sampling of lymph node metastases was undertaken in 31 women.
Outcomes: To determine the rate of discordance of Her2 status between primary and metastatic cancer tissue.
Follow up: N/A
Results: Metastases were located in ascites (n=3), liver (n=4), lung (n=9), lymph nodes (n=3), pericardium (n=1), pleura (n=74), skin or soft tissue (n=3) or CNS (n=8). Her2 status of primary and metastatic sites was concordant in 92.4% of the 105 patient samples ($\kappa = 0.76$ 95%CI: 0.61-0.92). When discordant pairs were re-examined this figure rose to 97.1% ($\kappa = 0.85$ 95%CI: 0.73-0.98). Her2 amplification occurred in 22/105 primary tumours and 21/105 paired distant metastases. Her2 status differed from primary to metastases in 8/105 pairs. These 8 cases were re-analysed: Her2 –ve (primary) to +ve (metastases) change occurred in 2 patients and Her2 +ve (primary) to –ve (metastases) change occurred in 1 patient. All other discrepancies were explained on the basis of borderline scoring of tissue one way or the other and were resolved on re-examination.
General comments: This paper describes a three centre study comparing the Her2 status of primary and metastatic tissue from women with breast cancer. The specimens were collected between 1999 and 2006. Tumour tissue was graded (nuclear grade I-III) by tissue micro-array and Her2 status was determined by FISH. The rate of concordance between paired tissue samples was analysed with the κ coefficient where a value of >0.8 was 'excellent' and 0.61-0.8 was 'substantial'. The authors point out that, on the basis of FISH analysis, discordance occurred in 7.6% of patients. Given that the level of re-investigation undertaken in this study would be unlikely to occur in a clinical situation, there could be a risk of both under- and over-treatment for some patients. Inconsistencies between the paired samples were generally due to interpretational differences rather than actual biological conversion by clonal selection or genetic drift during progression.

Santinelli <i>et al.</i> (2008)
Design: Retrospective case series, evidence level 3 Country: Italy
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 119, age range 26 to 76 years, mean age = ~53 years
Interventions: Paired biopsy samples from a primary cancer and: Group A: synchronous lymph node metastases (n=45) Group B: metachronous lymph node metastases (n=9) Group C: local recurrence (n=30) Group D: metachronous distant metastases (n=35) were processed for determination of Her2 status by fluorescent <i>in situ</i> hybridisation (FISH) and immunohistochemistry (IHC Hercep Test). The degree of amplification was assessed by two independent

expert pathologists using a double blind method. Discordant results were discussed at a conference microscope.

Outcomes:

To determine the rate of discordance of Her2 status between primary and metastatic cancer tissue.

Follow up:

N/A

Results:

Group A (n=45):

Her2 -ve (1+) primary: 1/7 discordance (85.7% concordance)

Her2 +ve (2+) primary: 1/9 discordance (88.9% concordance)

Her2 +ve (3+) primary: 1/14 discordance (92.9% concordance)

Summary: 3/45 cases (6.7%) were Her2 +ve in primary and normal in metastases

Group B (n=9):

Her2 -ve (0) primary: 0/5 discordance (100% concordance)

Her2 +ve (2+) primary: 0/2 discordance (100% concordance)

Her2 +ve (3+) primary: 0/2 discordance (100% concordance)

Group C (n=30):

Her2 -ve (0) primary: 3/20 discordance (85% concordance)

Her2 +ve (2+) primary: 1/3 discordance (66% concordance)

Summary: 4/30 cases (13.3%) were normal in primary and Her2 +ve in metastases

Group D (n=35):

Her2 -ve (0) primary: 1/14 discordance (92.9% concordance)

Her2 -ve (1+) primary: 2/3 discordance (33% concordance)

Her2 +ve (2+) primary: 6/12 discordance (50% concordance)

Her2 +ve (3+) primary: 1/6 discordance (83.3% concordance)

Summary: 6/35 cases (17.2%) were normal in primary and Her2 +ve in metastases and 3/45 cases (11.4%) were Her2 +ve in primary and normal in metastases.

General comments:

This paper describes a single centre study comparing the Her2 status of primary and lymph node metastases or distant metastatic tissue from women with breast cancer. The metastatic tissue specimens were collected prospectively between 2001 and 2006 and then compared with archived tissue from the corresponding primary cancer. Her2 status was determined by FISH and IHC.

14/65 (21.5%) cases showed a therapeutic, significant ($P < 0.001$) discordance of Her2 status between primary and local recurrence or distant metastases. In 10 cases amplification occurred in the relapse but not in the primary tumour and vice versa in 4 cases. These results led the authors to suggest that Her2 testing should be performed with tissue from the metastatic site in order to determine candidacy for trastuzumab treatment.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Chapter 3 – Providing Information and Support for Decision Making

3.1 The use of (1) decision aids and (2) information tools to improve treatment outcomes and quality of life

3.1.1 Decision aids

Short summary

Two systematic reviews (O'Brien *et al.*, 2002 and O'Connor *et al.*, 2002) and two RCTs (Siminoff *et al.*, 2006 & Davison and Degner, 2002) provided evidence for the use of decision aids. All were recent papers and of high quality. The majority of study participants had breast cancer.

The reviews showed that decision aids were effective for patients in their decision making, better than standard care for patients to gain knowledge and realistic expectations and better than standard care in reducing indecision, conflict and passivity. However, decisions aids made no significant difference to patients' satisfaction with their decisions or treatment choice and had no effect on health related outcomes such as anxiety or quality of life

Good evidence showed that giving patients the choice of assuming a passive, active or co-operative role in making treatment decisions with their clinician had a greater influence on treatment outcomes than the actual choices themselves.

A personally tailored software tool (Adjuvant!) giving breast cancer patients their 10-year prognosis, depending on case history and choice of adjuvant therapy, was significantly more influential on decision making than a generic pamphlet without data.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Individuals with advanced breast cancer	Decision aids (as defined in Cochrane review)	Not using decision aids	<ul style="list-style-type: none"> • Knowledge • Empowerment • Satisfaction (with process of making decision, decision made & support in decision making) • Change in treatment pathway • Levels of regret, anxiety & depression • QOL • Overall survival • Communication with health professionals • Physical and social functioning

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence statement

Four papers addressed the question of decision aids – two systematic reviews (O'Brien *et al.*, 2002 and O'Connor *et al.*, 2002) and two RCTs (Siminoff *et al.*, 2006 and Davison *et al.*, 2002) from the USA and Canada.

O'Brien *et al.* (2002) conducted a systematic review of 39 studies (including 16 RCTs) in which was an assessment of a variety of decision aids including pamphlets, audiotapes, videotapes, interactive computer software, educational scripts, decision boards, counselling and decision analyses. It is not known how many, if any, of these interventions are on the Cochrane list of decision aids. Unfortunately, the review authors found the quality of included studies to be only weak from the point of internal validity (i.e. a causal relationship between intervention and outcome).

However, they concluded that decision aids were generally useful in terms of involving the patient in decision-making (but not with regard to treatment) and increasing their understanding of the issues without adding to their anxiety and depression. This was a good study which searched all the relevant databases up to 2000/1 and was not restrictive in the choice of material.

O'Connor *et al.* (2002) published a very high quality (Cochrane) systematic review on decision aids evaluated by the CREDIBLE criteria (developed as part of the Cochrane Systematic Review of Patient Decision Aids to provide a summary of some key indicators that provide confidence in the credibility of decision aid content). Unfortunately, only two of the included studies related specifically to breast cancer patients and these studies were looking at decisions about treatment for early disease but the review paper was included for general background.

The authors found that decision aids performed better than standard care in terms of gaining patient knowledge, developing realistic expectations, lessening decisional conflict, reduction of passivity in decision-making and indecision. However, the decision aids made no significant difference to satisfaction with the decisions made or with the treatment choice, health related outcomes such as anxiety, or quality of life.

Siminoff *et al.* (2006) presented a RCT of 405 patients which evaluated a computer software program called Adjuvant! This intervention was a decision guide which gave the user an estimate of outcomes and prognosis for each adjuvant treatment choice, either chemotherapy, endocrine therapy or a combination. By using the patient's own case history the outcomes were tailored to the patient and presented as a 10 year risk profile. The issue of side effects were dealt with by the clinician at the time of interview and at the same time as presentation of the intervention. The comparator group received generic information in a leaflet and this was presented in the same format as the intervention but without the personalised forecast and graphs.

The follow-up questionnaires were completed 3 months after the clinic appointment and revealed that patients who were primary decision-makers were less likely to have wanted adjuvant therapy. Others who did not take adjuvant therapy included those patients treated in the academic rather than community setting, those who had node negative breast cancer, who had received the intervention, who preferred an autonomous role in decision making or were post-menopausal. Nearly half the patients found the aid to have been influential on the decisions that they had made. Some of these patients had advanced disease.

Davison *et al.* (2002) presented a Canadian RCT assessing the use of computer software to elicit patient preference for control over decision-making during a clinical appointment. By a stepwise elimination process, the patient arranged in order of preference five scenarios depicting their degree of involvement. By comparing the selected outcome with that of the actual clinical appointment it was possible to determine how many women were able to achieve their preferred role in their meeting with the clinician. The control group was given the same preference scale but

had to perform the exercise without a computer. The discussions that they had with their clinician were of the same duration and content as that of patients in the intervention group.

The intervention did not prove to be of significance in the assumption of the preferred role between the two arms. The exercise did demonstrate that more women aged over 50 years took a passive role in decision making and it also provided information about decision making in general, regardless of intervention. The authors make the statement that in their opinion it is not the actual role that patients take in their treatment planning that is of prime importance but rather that outcomes are improved if a woman is given the opportunity by the clinician to assume her chosen role, whether passive, active or co-operative.

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Evidence tables

Question: Effectiveness of decisions aids as defined by Cochrane review
Created by: Karen Francis on 22/05/2007

O'Brien <i>et al.</i> (2002)
Design: Systematic review of RCTs (therapy), evidence level: 1++ Country:
Inclusion criteria: Study participants: Adults (not defined) Cancer patients Physicians Papers included: Non-English language papers
Exclusion criteria: Participants excluded: Patients using DA for HRT, benign prostatic hyperplasia or smoking cessation Papers excluded:

<p>Papers describing DA aimed solely at the physician Papers in abstract form or unpublished</p>
<p>Population: -</p>
<p>Interventions: Any decision aid (DA) when defined as an intervention to help patients (with or without their physicians) to make cancer-related health care decisions when there are options for screening, prevention or treatment.</p> <p>Effectiveness studies examined pamphlets, audiotapes, videotapes, interactive computer programs, educational scripts, decision boards or counselling and informal decision analysis.</p>
<p>Outcomes: No specific outcomes but mainly included: Patient decisions; Knowledge; Anxiety; Depression; Satisfaction; Acceptability of the DA were the most common outcomes.</p>
<p>Follow up: -</p>
<p>Results: 39 studies were identified that evaluated a DA in a clinical context. 16 were RCTs, 4 were non-randomised trials, 2 were cohort studies, 6 were pre-/post- test design and 11 were case series. Studies were not pooled due to heterogeneity. Breast (23) and prostate cancer (11) were the most frequent types of cancer.</p> <p>Using the three scales for judging the quality of RCTs, papers were found to be generally weak in the area of internal validity. They found that overall, DAs increased knowledge and patient involvement in decision making. Anxiety and depression scores were not apparently increased. The cohort studies showed that DAs decreased decisional conflict or uncertainty and had an influence on decision making.</p> <p>Authors concluded that decision aids appeared to be helpful without increasing anxiety or depression, particularly for screening, but there was a lack of evidence relating to effectiveness for decisions relating to treatment.</p>
<p>General comments: This systematic review examined the efficacy of DA on a variety of outcomes. Most of the reviewed papers (33/39) concerned either breast or prostate cancer patients.</p> <p>Databases searched included: MEDLINE (1977-2001), HealthSTAR, CINAHL, Sociological Abstracts, PsycINFO (1977-2000), EMBASE (1995-2000) and the Cochrane Library. Search terms were given.</p> <p>Validity of papers was assessed using the Jadad scale, the Down and Black scale and the Guyatt scale. 7 reviewers screened all papers such that each paper was assessed by 2 reviewers and any disputes were resolved with the help of a third reviewer. Data were extracted by 2 reviewers using forms designed in-house. Discrepancies were resolved by consensus.</p> <p>The literature search was thorough and unrestricted. There may have been publication bias as unpublished papers were excluded. The research team used a two-stage screening process. In the first step, six raters worked in pairs to screen the titles and abstracts identified by the searches. In the second step, randomly assigned pairs of raters screened full text articles, then three reviewers checked all included studies and categorized them according to the context of the decision and type of study. Discrepancies were resolved by discussion. The schemes of screening, reviewing and resolving differences suggest a lack of review bias.</p>

The heterogeneity of the included studies suggests that authors conclusions may be only broadly applicable and that information from individual studies should also be reviewed.

O'Connor *et al.* (2002)

Design: Systematic review of RCTs (therapy), evidence level: 1++

Country:

Inclusion criteria:

Decision aids included those with:

- a) Publication information
- b) Developer information
- c) Source of funding/sponsorship
- d) Timing of publication: year(s) of publication; update policy
- e) Potential users: target audience; skills required
- f) Delivery method: medium, level of interactivity, use in relation to counselling
- g) Elements of the decision aid
- h) Practitioner support: inclusion of materials or tools to guide practitioners in using decision aids with patients
- i) Development process: use of needs assessment, evidence reviews, expert review panels, and user review panels
- j) Evaluation data
- k) Publications list.

All decision aids identified were assessed using the CREDIBLE criteria for quality of development and evaluation of decision aids (Stacey 2001)

Included studies:

All studies using a RCT design comparing decision aids to no intervention, usual care, alternative interventions, or a combination.

Included participants:

Over the age of 14

People making decisions about screening or treatment options for themselves, for a child, or for an incapacitated significant other.

Exclusion criteria:

Interventions that focused on decisions about lifestyle changes, clinical trial entry, or general approaches to treatment if the person should become unable to participate in decision-making in the future; education programs not geared to a specific decision; and interventions designed to promote adherence to or to elicit informed consent regarding a recommended option, were excluded from the analysis.

Papers excluded:

Studies not focused on making a choice

Studies where the intervention offered no decision support in the form of a decision aid

Studies where the decision was hypothetical with participants not actually at a point of decision making.

Population:

-

Interventions:

Decision aids were defined as interventions designed to help people make specific and deliberate choices among options (including the status quo) by providing (at the minimum) information on the options and outcomes relevant to a person's health status.

The aid may have included:

Information on the disease/condition, costs associated with options, probabilities of outcomes tailored to personal health risk factors, an explicit values clarification exercise, information on others' opinions, a personalized recommendation on the basis of clinical characteristics & expressed preferences and guidance or coaching in the steps of decision making and in communicating with others.

Outcomes:

Presence of communication between people and practitioners
Decisional conflict
Knowledge
Realistic expectations
Clarity of values
Agreement between personal values for outcomes and choice
Implementation of preferred choice
Satisfaction with the decision, the decision making process and the decision support provided
Actual choice made
Health related quality of life
Adherence to the chosen option
Resource utilization
Emotional distress
Anxiety
Depression
Regret
Litigation rates.

Follow up:

-

Results:

34 RCTs were evaluated in this high quality, generic systematic review in which 31 different decision aids were covered. Most are intended for use before counselling. Only 2 RCTs focused on breast cancer (both related to decision aids about surgery) but, due to the thorough nature of this review, the results for all studies are presented.

Using the CREDIBLE criteria to evaluate the quality of the decision aids:

- Most included potential harms and benefits, credentials of the developers, description of their development process, update policy and were free of perceived conflict of interest
- Many included reference to relevant literature
- Few included a description of the level of uncertainty regarding the evidence
- Few were evaluated.

Overall Results for all trials:

Among the trials comparing decision aids to usual care, decision aids (DA) performed better in terms of:

a) Knowledge

DA (compared to usual care) had significantly higher average knowledge scores with gains of 9 - 30 points. Weighted mean difference (WMD) = 19 points (95% CI: 13-24). Note: The WMD or 'difference in means' is a standard statistic that measures the absolute difference between the mean values in the two groups in a clinical trial. It estimates the amount by which the treatment changes the outcome on average.

Detailed DA (compared to simpler DA) had a statistically significant greater knowledge gain with WMD = 4.4 points (95%CI: 2.4-6.2). This analysis included both BC RCTs neither of which

individually showed any statistical difference between intervention and comparator.

b) Realistic expectations

The pooled relative risk of having more realistic expectations (reported by way of measuring perceived probability of outcomes) after using a DA compared to usual care was 1.4 (95%CI: 1.1-1.9).

The pooled relative risk of having more realistic expectations after using a detailed DA compared to a simpler DA was 1.5 (95%CI: 1.3-1.7)

c) Decisional conflict

Lower decisional conflict related to feeling informed was the most consistently observed effect of DA compared to usual care. A statistically significant reduction in feeling uninformed about options, benefits and harms by 5 to 16 percentage points (pooled WMD -9.1 of 100 (95%CI: -12 to -6).

No statistically significant reduction for feeling uninformed about options, benefits and harms was observed between detailed and simpler DA.

d) Participation in the decision making process

Five out of seven studies showed a 26-70% reduction in the proportion of people who assumed a passive (practitioner- controlled) role in decision making with two trials that were statistically significant and three that were not. The other two studies showed no difference. The pooled RR = 0.7 (95%CI: 0.5-0.9).

For individuals assuming an active (patient-controlled) role in decision making three of the seven studies reported relative risks ranging from 2.8-7.6, indicating a significant impact on the assumption of the patient-controlled role, two indicated an increase that was not statistically significant, and there was no difference for the other two studies (pooled RR = 1.49 95%CI: 0.99-2.25). The proportion adopting a shared decision making role was more variable (pooled RR = 0.9 95%CI: 0.7 to 1.1)

e) Proportion undecided

The studies reporting on the proportion of people who remained undecided post intervention showed statistically significantly lower proportion in the decision aid group. The pooled RR = 0.43 (95%CI: 0.3 - 0.7).

Decision aids appeared to do no better than comparators in affecting satisfaction with decision making, anxiety, and health outcomes and had a variable effect on which healthcare options were selected.

General comments:

Overall conclusions about the effectiveness of DA are restricted because of the variability in the decision context (screening, disease), the design used, the comparison used in the evaluation, outcomes included and the measurement of them. In spite of these limitations, the trials consistently demonstrated that DA do better than usual care interventions in improving people's knowledge regarding options (19% absolute improvement), enhancing realistic expectations about the benefits/harms of options (40% relative improvement), reducing their decisional conflict, decreasing the proportion of people remaining undecided, and stimulating people to take a more active role in decision making.

Compared to simpler versions, DAs improved knowledge only marginally, but had other benefits such as increasing realistic expectations and agreement b/n values and actual choices. The impact of DAs on increasing or decreasing references for particular options is more variable, which might be expected given the balanced information presentation within the DA and potentially variable preference rates at baseline. The review points out that most studies report

that DAs reduced people's enthusiasm for major elective surgery in favour of more conservative options.

There has been no impact on satisfaction with the decision making process or with the actual choice, nor has there been an impact on health outcomes such as anxiety, general quality of life, or condition-specific quality of life.

There are too few studies to determine effects of DAs on persistence with the chosen therapy, costs, resource use, or efficacy of dissemination strategies.

Davison & Degner (2002)

Design: Randomized controlled trial (therapy), evidence level: 1+
Country: Canada (federal state, Commonwealth Realm)

Inclusion criteria:

Diagnosed with breast cancer
 Ability to read and write English
 No evidence of mental confusion

Exclusion criteria:

None stated

Population:

Number of patients = 749.

Interventions:

Intervention (n = 367):

A computer program consisting of two measures:

(1) Control Preferences Scale to elicit patients' preferences for control over decision making, from active to passive. This consists of 5 statements about roles which are presented on screen in pairs. The patient selects one option from each pair continuing the process until the point where all 5 options are then ordered.

(2) A pencil and paper survey questionnaire of 9 information categories: chances of cure, spread of disease, side effects, treatment options, social activities, effect on family, family risk, home self-care and sexuality.

Comparator (n=367):

These patients did not use a computer program. They were offered the Control Preference Scale and asked to select 1 of the 5 options about their preferred role in decision making. The patient also discussed general issues for the same length of time as patients using the intervention (~15 min).

Outcomes:

To evaluate the effect of a computer assisted intervention intended to enhance communication between patient and healthcare professional. The study examined (1) the extent to which patients achieved their preferred decisional roles and (2) satisfaction with their clinical medical appointment.

Computer program results were produced in the form of a print-out which the patient could use as a prompt sheet in the consultation with her physician. This would remind her of the level of responsibility for decision making which she had selected and the area of particular concern that she wished to discuss.

Follow up:

NA

Results:

After the interview with their physician, all patients were asked to pick the option from the Control Preference Scale which best described the decision making role that they did assume during their clinical visit. They also completed a 14 point Patient Satisfaction Questionnaire using a 5 point Likert-type scale: a total of 60 indicated 'low satisfaction' and 14 indicated 'high satisfaction' with their clinic visit.

The intervention and control groups were, according to the authors, 'remarkably similar' - no statistically significant difference in demographics between the two arms was identified.

80.1% of all patients preferred to take an active or collaborative role in decision making.

72.6% of patients assumed their preferred roles.

Before the consultation with their physician, a significantly higher proportion of patients in the control group, compared to the intervention group, stated that they had a preference to adopt a passive role in decision making (23.7% vs 16% P = 0.16). However, there was no significant difference between the arms in the number of women that did assume that role during the consultation (30.5% vs 27.5%).

The proportion of women in the intervention group that indicated a desire to take a passive role (16%) was significantly lower than those women who did adopt this role during the consultation (27.5% P < 0.0001).

A higher proportion of women > 50 years reported a preference to play a passive role in decision making.

Patients did not differ significantly in their response to the 14-item questionnaire and both groups were satisfied with their clinic visits.

General comments:

This paper describes a RCT which was conducted with breast cancer patients recruited from 3 oncology centres in one Canadian State. The patients represented a 'convenience sample', a group of people under study who have been assembled based on the ease of interviewing them or on accessibility to their records, etc. While this type of sampling can help produce good information about a topic, its major disadvantage is that there is no way of knowing if the group is representative of the population as a whole. The authors did state that the demographics were consistent with those of the underlying population of Manitoba, Canada.

Block randomisation was done before data collection to maintain equal numbers of patients in the intervention and comparator groups. Subjects were assigned in the order of accrual. Assignment was concealed from patients by using separate consent forms. This may have been because only the women using the intervention accessed a computer so blinding was not feasible.

Appropriate statistical methods were used to analyse the data (Chi-square and t-tests).

The authors conclude that in their opinion it is not the fact that women take an active role in decision making that leads to better outcomes but rather that women take the role that they prefer to take, whether active or passive, that leads to better outcomes.

Siminoff *et al.* (2006)

Design: Randomized controlled trial (therapy), evidence level: 1+

<p>Country: United States</p>
<p>Inclusion criteria: Diagnosed with breast cancer Completed primary surgical treatment Were candidates for adjuvant therapy No prior history of breast cancer Written informed consent from patient and physician</p>
<p>Exclusion criteria: Stage IV cancer Significant co-morbidities requiring chemotherapy DCIS or inflammatory breast cancer</p>
<p>Population: Number of patients = 405, mean age = 62 years.</p>
<p>Interventions: Intervention (n = 171): Computer software called Adjuvant! a decision guide that provides estimates of outcomes with or without adjuvant therapy (AT). This program produces coloured graphs of 10-year outcomes expected depending on intervention chosen i.e. surgery, chemotherapy, endocrine therapy or combined chemo- and endocrine therapy.</p> <p>Outcomes present as risk reductions talking into account the individual's disease and the known effects of the particular therapy. Estimates of prognosis are based on the Surveillance Epidemiology and End Results Registry outcomes (produced in the USA). Estimates of efficacy are obtained from the Early Breast Cancer Trialist's Collaborative Group RCT results.</p> <p>Comparator (n = 234): Information leaflet based on several common informational pamphlets and providing general information about adjuvant therapy, rationale and treatment options. It contained no numeric information but was presented in the same colours and format as the intervention.</p> <p>Physician's practices were stratified (community or academic) and then randomised to receive the intervention or comparator which was then given to the patient by the physician at the first post-surgical oncology consultation. All patients had side effects discussed with them by the physician as part of a normal procedure which included history taking and clinical examination.</p>
<p>Outcomes: To determine if patients, having seen a numerical estimate of the benefit of a particular treatment, would make different decisions than patients who had received only a pamphlet. The measure of patient preferences was obtained using the Decision Making Preference Questionnaire (DMPQ). This categorised the outcomes as (a) physician makes the decision (b) patient makes the decision or (c) the decision making is shared.</p> <p>To determine if the patients disease stage would influence their decision making.</p>
<p>Follow up: Both patients and physicians were asked to complete questionnaires in order to rate their experience with the intervention.</p> <p>Patient records were checked after 3 months to determine which intervention the patients were receiving.</p>
<p>Results: 43.7% patients received care in the community and 56.3% received care in an academic setting.</p> <p>176 patients chose hormonal treatment only</p>

107 patients chose combined hormone and chemotherapy
68 patients chose chemotherapy only
54 patients chose not to take adjuvant therapy of any type
Options chosen were not statistically different between intervention and comparator arms (P = 0.6)

Influence of disease stage: intervention vs comparator

Node –ve, treatment = 76.1% vs 85.5%
Node –ve, no treatment = 23.9% vs 14.5% (P = 0.06)
Node +ve, treatment = 97.8% vs 98.2%
Node +ve, no treatment = 2.2% vs 1.8% (P = 1.0)

Node –ve, hormonal therapy = 49.3% vs 40.2%
Node –ve, no hormonal therapy = 50.7% vs 59.8% (P = 0.8)
Node +ve, hormonal therapy = 69.6% vs 88.9%
Node +ve, no hormonal therapy = 30.4% vs 11.1% (P = 0.008)

Node –ve, chemotherapy = 89.4% vs 88.0%
Node –ve, no chemotherapy = 10.6% vs 12.0% (P = 0.8)
Node +ve, chemotherapy = 51.1% vs 38.9%
Node +ve, no chemotherapy = 48.9% vs 61.1% (P = 0.2)

Bivariate analysis:

Patients who did not choose to take adjuvant therapy:

- (1) tended to prefer the role of primary decision maker whereas patients who did take adjuvant therapy tended to prefer shared decision making with their physician (P=0.01).
- (2) were more likely to have been treated in the academic setting than in the community (P<0.0001).
- (3) mainly had node –ve, smaller (< 2cm) tumours (P = 0.003).

Multivariate analysis:

Patients were less likely to take adjuvant therapy:

- (1) if they had received the DA (OR = 0.32 P=0.02)
- (2) if they preferred to take a more autonomous role in decision making vs sharing the decision making (OR = 2.38) or letting the physician decide (OR = 1.83 P = 0.02)
- (3) if they had smaller tumours (OR = 0.12 P =0.02)
- (4) if they had no positive nodes (OR = 0.11 P < 0.0001)
- (5) if they had estrogen receptor +ve tumours (OR = 2.5 P = 0.009)
- (6) if they had gone through the menopause (OR = 4.63 P = 0.02).

Patients that had received the DA found it more helpful and more influential on decisions made. 54.5% patients in this group gave it the highest rating compared with 34.4% of the control group's who rated the pamphlet similarly. 59% of patients in the intervention group rated the DA as either 'helpful' or 'very helpful' compared to 38.7% of control patients.

General comments:

This paper describes a RCT comparing a computer decision aid (DA) against a pamphlet. Both were designed to assist patients in deciding what adjuvant treatment, if any, would give the most benefit to them based on their clinical data and epidemiological statistics. The trial was conducted from 1998 to 2001 at 14 GP practices in the USA.

This paper was included in the review since some of the patients had stage III breast cancer.

An analysis of patient characteristics between arms showed that there were more patients from minority groups in the treatment arm but there no significant differences between arms in respect of education, income, disease state or insurance cover (USA). There were more female doctors

in the intervention group practices (43% vs 23%).

Statistical analyses (Kendall's tau-b, Fisher Exact, median test, logistic regression) explored bivariate relationships between the decision whether or not to take the treatment and independent variables.

Note that the physician's practices were randomised but patients were not. This means that patient data would have been analysed in clusters from each practice and for this reason this variable was considered as a random effect whilst all others were considered fixed.

Analyses which refer to income and the likelihood to take or not to take adjuvant therapy are omitted here since expense is unlikely to be a factor for patients in the UK.

Integrating the probability of side effects from treatment into this model may have changed the outcomes.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

3.1.2 Information tools

Short summary

The evidence on patient information comprised one systematic review (Gaston and Mitchell, 2005) and five RCTs (Winzelberg *et al.*, 2003, Jones *et al.*, 2006, Williams and Schreier, 2005, Aranda *et al.*, 2006 and Walker and Podbilewicz-Schuller, 2005). RCT evidence focused broadly on person to person interventions, written information or audiovisual aids.

The review found that patients with advanced disease often required as much information from their clinician as patients with early breast cancer but the desire for involvement with treatment decisions sometimes declined as disease progressed. The review found consultation tapes to be effective but general information tapes, although well received, occasionally caused confusion. Written information was only effective if pitched at the appropriate educational level for the patient. Question prompt sheets were useful and resulted in better consultations whilst giving the patient written information to take home improved communication with the family.

A web-based support group significantly reduced levels of depression, stress and anxiety in users when compared with controls. However, a nurse-led intervention of active listening, empathy and support together with provision of information cards tailored to the patient's need and coaching in self-care, stress reduction and communication was only effective for women with high initial psychological needs.

Information booklets supplemented by a patient's own clinical information were thought more likely to tell the patient something new and were considered less limited in scope when compared to a generic booklet. Patients found an automatically selected range of breast cancer literature more informative and less overwhelming than a number of self-selected booklets chosen from a computer generated list.

An audio tape of education about exercise and relaxation as a means to combat anxiety, fatigue and sleep problems associated with chemotherapy, together with a self-care diary, reduced the increase in patient-reported anxiety as treatment progressed when compared with standard care. A videotape plus a list of basic questions to be asked at a multi-disciplinary team consultation, when added to standard written information, made no significant impact on depression, patient anxiety, quality of life or feelings of helplessness/hopelessness.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Individuals with advanced breast cancer	Information tools for example DVD, written material, face to face meetings (such as contact with other breast cancer patients, or support groups), courses, audio, video, websites, interactive and the more usual static types, nurse specialist or other MDT member)	<ul style="list-style-type: none"> • Standard care • Each vs each other 	<ul style="list-style-type: none"> • Knowledge • Satisfaction with decision made • Empowerment • Treatment pathway changed • Satisfaction with process of making decision • Reduction in anxiety, regret depression • QOL • Overall survival

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence statement

This evidence base consists of one systematic review from Australia and four RCTs, three of which are from the USA and only one from the UK. None of the papers dealt specifically with advanced breast cancer patients and this is likely to affect the applicability of the data to the population of interest.

There is little consistency between papers since each study looks at a different information source. However, these tended to be generally well received by the participants and were effective to some degree in allaying anxiety and depression. None of the papers included a long follow-up period and so it was not possible to determine if overall survival or changes to the treatment pathway were affected as a result of exposure to the interventions.

The systematic review (Gaston and Mitchell, 2005) was appraised because, although not a high quality paper, it dealt with patients who had advanced cancers, many of which were probably of the breast, and examined information giving as well as broader issues of patient involvement in decision making. The authors reviewed 47 papers, including controlled, uncontrolled and descriptive studies but rejected non-English papers and those of lesser quality (<2 on Jadad scale). The total patient number of the included studies was over nine thousand.

The main conclusions from this work are that patients with advanced cancer often have as much of a requirement for information from their clinician as early cancer patients do but that the desire for involvement with treatment decisions may decline as their disease progresses. The majority of patients in palliative care wished to be involved in decision-making to some degree but follow-up studies showed that in reality this had not happened for many of them, an outcome that negatively correlated with feelings of satisfaction.

Many patients misunderstood the extent of their disease, the prognosis or the aim of their therapy or were ill-informed or had forgotten or rejected the content of the information that they had received. The lack of understanding may have arisen because clinicians had not given the patient sufficient information due to constraints on their time or from a desire to protect patients from bad news. Although this was counter intuitive to the authors, there was no evidence that giving patients more information, even about a poor prognosis, and involving them in the management

of their disease destroyed hope - rather it empowered the patient and even reduced their anxiety levels in some cases.

When specific interventions were reviewed it was found that consultation tapes had increased the patients' knowledge and had given them more satisfaction with their clinical appointments. General information tapes were not so well received and occasionally caused confusion amongst some groups. However well informed patients were by tapes, their overall satisfaction or quality of life was not improved but this was still a preferred medium compared with written materials. Information in pamphlets or brochures was only effective when pitched at or below the educational level of the target audience.

Question prompt sheets, either generalised or personalised to the patient, were effective, especially when computerised, and led to an increase in enquiries from patients about their prognosis. Even though clinicians expressed concerns about this outcome, the consultations actually became more effective, did not take any longer and did not adversely affect the patients' anxiety levels. Written materials provided to the patient to take home with them were considered to be very beneficial and increased communication between the patient, family and friends which in turn helped to facilitate better emotional and practical support. The benefits of personalised information provisions might have to be balanced against the possible increase in workload to the clinician.

The RCTs reported on outcomes for four different interventions: a web-based support group (Winzelberg *et al.*, 2003), a video presentation (Walker and Podbilewicz-Schuller, 2005), an audiotape and self care diary (Williams and Schreier, 2005) and printed information booklets (Jones *et al.*, 2006)

Winzelberg *et al.* (2003) reported on a 12 week, structured, web-based support group called 'Bosom Buddies' to which 36 women were subscribed. The group was moderated by a mental health professional that directed participants to the selected subject matter but did not offer medical opinions except in an emergency. The subjects under discussion included different elements of the patient pathway and also provided information in some cases. A comparator group received no intervention but were all on a waiting list to join the Bosom Buddies group. The outcomes mainly centred on psychosocial issues such as dealing with family and friends, coping strategies, romance and sexuality etc. However, this study was appraised since there was an element of information-giving to patients and from which they may have derived some benefit. The response to the intervention was measured on many accepted scales including those for anxiety, post-traumatic stress, depression and perceived stress. In addition, the participants completed a questionnaire about their impressions of the support group and how it had helped them.

At the close of the study, the intervention group scored significantly less on measures of depression, post-traumatic stress and anxiety but were no different from the comparator group in all other outcomes. The group was popular with 55% of participants rating it as being of great value for getting advice.

Jones *et al.* (2006) presented a complex RCT of 400 UK patients randomised to receive one of three interventions (or their individual comparators): General information in the form of CancerBACUP booklets with or without personalised information from patient's case files; Information chosen by the patients from a prepared list on a computer at the oncology centre or an enhanced volume of written material without computer access; Additional anxiety management advice or none. The eight possible combinations of intervention were tested by follow-up patient questionnaires to assess their influence on anxiety and depression, requirement for social support and to understand information needs.

The findings were complex but, briefly, patients who selected their own written information most commonly chose booklets on diet, understanding breast cancer, radiotherapy and complementary

therapy. Patients randomised to receive automatically selected reading, as opposed to patient selected texts, found the content more useful and less overwhelming. Booklets with additional personal information were preferred over general information as they were more likely to tell the patient something she didn't know and were also considered to be less limited in scope. No particular arm scored any higher than the rest with respect to improving the patients' understanding of cancer and by the end of the follow-up period most patients reported no change (58%) or an improvement (34%) in their comprehension of the subject.

Patients who received booklets with personalised information were more likely to share the contents with confidants either in or outside of their family and also considered that the information had helped them to discuss their disease or its treatment with others. Unexpectedly, however, this group also reported a higher level of negative interactions than those receiving automatically selected reading material.

Williams and Schreier. (2005) presented data from a RCT of 71 breast cancer patients (most of whom did not have stage III or IV disease) which assessed an audio tape of education about exercise and relaxation as a means to combat anxiety, fatigue and sleep problems associated with chemotherapy. The audio tape was accompanied by a self-care diary which included details of appropriate self-care behaviours. The comparator group received standard education and care which was also given to the intervention group. At baseline and after 1 month and 3 months, participants completed questionnaires to assess the outcomes of interest and also to rate the efficacy of the self-care behaviours and the frequency with which they were used. They were also asked to report the number and severity of chemotherapy side effects that they had experienced.

Whilst patient-reported anxiety increased over time in both groups, the increase was significantly greater in the comparator group. The intervention group reported the use of a much higher number of self-care behaviours relating to anxiety and rated them all as being effective. However, more women in the intervention group reported fatigue, although levels rose in both groups with time and neither group used more self-care behaviours than the other. More women in the comparator group reported problems with sleep and the severity of this problem increased for both groups over time. Women in the intervention group did not find the self-care behaviours for sleep problems effective with the one exception which related to 'trying not to think about side effects'. The groups did not differ in the number or severity of reported side effects.

Walker and Podbilewicz-Schuller, (2005) assessed a video presentation called 'A Guide to Your Visit'. This was a professionally produced film which portrayed a sequence of events representing what the patient might experience on their first visit to a multi-disciplinary team (MDT). Careful design of this product ensured that the more realistic 'coping' aspect of the patient's experience, rather than a mastery of the situation, was portrayed. To accompany this tape, patients were supplied with written information and a list of basic questions which they might wish to ask the MDT. A comparator group received this same written information but no video and no list of questions. Ten days after their clinic visit participants reported the outcomes by completing several standard questionnaires to assess anxiety, depression, helplessness/hopelessness and quality of life. These were compared with baseline responses which showed that there were no fundamental differences between the two arms in terms of participation in decision making or satisfaction with their appointment. There were some correlations between use of the video and minority status, marriage status and mental health which all found in favour of the intervention. Unfortunately this study only recruited relatively low numbers of participants such that sub-group analyses of this type would be likely to have been underpowered.

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Evidence tables

Question: Effectiveness of information tools
Created by: Karen Francis on 22/05/2007

Gaston & Mitchell (2005)
Design: Systematic review of RCTs (therapy), evidence level: 1- Country: Australia
Inclusion criteria: Key terms: advanced cancer, oncology, palliative, decision-making, patient participation. Included papers: Articles concerning adults Full text English language RCTs Uncontrolled and descriptive studies 47 papers were reviewed and divided into four themes: Patient preference for involvement; Patient knowledge of diagnosis, Prognosis and aims of treatment; Improving participation in treatment decisions; Interventions to improve information giving.
Exclusion criteria: Excluded papers : Papers of quality <2 on the Jadad scale
Population: -
Interventions: Information sources and decision aids included: audio recording of consultation, individual patient summary, consultation tape, videotape of treatment information, booklet, computer programme, decision cards, decision board, question prompt list.
Outcomes: Patient preference for involvement Patient knowledge of diagnosis, prognosis and treatment Improved participation in treatment decisions Interventions to improve information giving.
Follow up: Details of follow-up and loss to follow-up are given.

Results:

What do patients want?

Advanced cancer patients demonstrated the same desire for information on their cancer as early cancer patients. Being informed gave a sense of control. Two third of patients in palliative care wished to be involved to some degree. The preference for involvement decreases with disease progression. Those patients who had been actively involved scored much less on a hopelessness scale.

Only a third of patients achieved a match between their perceived and achieved roles in the decision-making process. Role match was correlated with satisfaction.

Are patients adequately informed?

Studies revealed a widespread misunderstanding by the patient of the extent of disease, prognosis or the aims of the treatment. Patients had not, in many cases, been offered an alternative of supportive care as opposed to active treatment. The reasons for this lack of understanding might have resulted from poor information provision by the physician due to time constraints, poor consultation style or a well-meaning intention to protect the patient from bad news. Alternatively, some patients may have misunderstood, forgotten or rejected the information.

Interventions to improve information giving

Consultation tapes have been well received by various patient groups and have been shown to have a small but measurable improvement on knowledge and satisfaction with the encounter, an effect that might be age related. Tapes about cancer information in general were not so successful and could even cause confusion amongst their target audience.

However, a breast cancer RCT showed that tapes, whilst increasing the perception of having been well informed, did not affect overall satisfaction or quality of life. Tapes also compared well against individual patient information delivered in a written format - the latter also increased the clinician's workload considerably.

Written material must be appropriately pitched at the general population and the simplest books on chemotherapy scored highest on all criteria.

There was no evidence that giving patients more information increased anxiety levels and may even have improved them in some cases. However, again, the provision of written materials could cause problems with time in busy oncology clinics. Take home materials were of great benefit to patients who were then able to discuss issues with family and friends which facilitated practical and emotional support.

Interventions to encourage participation

The question prompt sheet enables the patient to get the information that s/he needs and is more personalised than standard aids, being more useful when endorsed by a clinician. A computerised version was very successful in a study of breast cancer patients.

Use of a prompt sheet has led to patients enquiring more about their prognosis, a situation that doctors had feared would increase anxiety or even prolong consultations but which have not had that effect and had instead made the consultation more effective.

General comments:

This paper describes a systematic review of the literature to identify studies that tested means of improving patient participation in decision-making and information provision to patients with advanced cancer (such that palliation, not cure, was the goal of treatment). This review is generic but was included in the evidence base because of its relevance to advanced disease and the probability that many of the population were being treated for breast cancer. The total number of patients in the included papers was 9,432.

Papers were identified from Pub Med (from 1966), PsycInfo (from 1967) and CINAHL (from 1982) - all up to 2003. Titles were reviewed by two authors with disagreement resolved by consensus.

There are few details of methodology and little in the way of a description of the overall quality of the included papers but each study is briefly summarised. No meta-analysis was conducted due to the subject matter and the type of studies that were reviewed.

Authors conclude that:

- (1) There is a need for patient information that might have been underestimated by doctors
- (2) Concealing a prognosis from a patient might remove their ability to make informed decisions about their treatment
- (3) Doctors might overestimate the degree to which patients have understood the information that they have been given
- (4) Being informed gives patients a sense of control, reduces anxiety, improves compliance and creates realistic expectations
- (5) Patients preferences for involvement in decision-making should be assessed not assumed
- (6) Patients involvement with decision-making may change through the course of their disease
- (7) Factors such as age, sex, educational level and cultural background are factors to be taken into consideration when understanding the patient's desired role in decision-making
- (8) Better information provision and giving opportunities to the patients to share in treatment decisions may require a shift in attitudes of clinicians that are accustomed to the traditional, paternalistic model of health care.
- (9) Sensitive informing and involving of the patient may not necessarily destroy hope but rather will involve the development of a more trusting co-operative attitude between patient and carer.

Jones *et al.* (2006)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United Kingdom

Inclusion criteria:

874 patients identified from outpatient appointment diaries as starting radiotherapy treatment for breast, prostate, cervical, or laryngeal cancer.

Exclusion criteria:

Receiving palliative care
 Severe pain
 Symptoms causing distress
 Cancer at other sites
 Receiving treatment for psychological or psychiatric problems
 Visual or mental handicap
 Case notes being unavailable, ambiguous or illegible.

Population:

Number of patients = 400, age range 28 to 82 years, mean age = 59 years, median age = 61years.

Interventions:

Participants were randomised to 8 groups defined by the three binary factors under study. Patients received either:

(a) General information from CancerBACUP (booklets: 'Understanding Radiotherapy', 'Diet and the Cancer Patient' and an appropriate cancer-specific booklet e.g. 'Understanding Breast Cancer') vs booklets plus additional personalised information, including data from patient's

medical records

(b) Information chosen interactively by patients themselves using a computer at the oncology centre vs a larger volume of material (40-47 sections) in booklets produced automatically but with no computer access

(c) Additional anxiety management advice (an extra set of pages with self help advice based on work in cognitive behaviour therapy for anxiety) vs none

Patients randomised to receive general information and who could select information interactively could choose sections from the above three booklets and from three further CancerBACUP booklets ('Cancer and Complementary Therapies', 'Feeling Better Controlling Pain', and 'Sexuality and Cancer'). Patients were allowed to choose up to 10 sections from a menu.

Patients randomised to receive personalised information and who could select information interactively could choose topics from their medical record such as 'Problem list', 'Treatment list', or 'Your cancer'.

For the patients who chose information interactively, sections chosen were recorded, and whether they required help with the computer, or whether they used the computer mouse or the touch screen.

Outcomes:

Identification of information needs (content and format)

Social support requirement , measured by Helgeson's social support questionnaire (HSSQ)

Anxiety and Depression levels, measured by hospital anxiety and depression scale (HADS)

Follow up:

Patients were sent follow-up questionnaires after 3 months including HSSQ, HADS and questions about their use and opinions of the booklets and reported understanding of cancer.

348/400 patients completed follow-up.

Results:

For the 199 participants who interactively selected information the average time spent using the computer (including explanation given by the researcher) was 9 minutes (range: 2-30). A third required help in using the computer; two thirds chose to use the touch screen, and a third used the mouse. Of the 82 (43%) patients who had not used a computer before, only two chose to use the mouse. The researcher operated the computer for four people. On average, patients chose eight sections (range 0-10); there was no difference by intervention or other factors.

The areas of information selected by BC participants (n=65) included:

From 'Diet and Cancer Patients': 'healthy eating' (n=23)

From 'Understanding Breast Cancer': 'possible causes' (n=21), 'living with surgery' (n=17)

From 'Understanding Radiotherapy': 'side effects' (n=19), 'general tips' (n=19), 'why prescribed' (n=18)

From Cancer and Complementary Therapies: 'feelings' (n=17)

3 month follow up:

Patient opinions of booklets and perceived understanding:

The booklets produced automatically, which were larger than those produced interactively by patients, were more likely to be found useful and to tell the patient something new and less likely to be seen as too limited, but they were also more likely to overwhelm some patients than the booklets produced interactively.

The booklets with personalised information were more likely than those with only general information to tell the patient something new. The patients given automatically produced booklets had higher overall satisfaction scores than those who produced their booklets interactively.

When asked to rate their current understanding of their cancer, 26 (8%) rated it less than they had done at recruitment, 188 (58%) rated it the same, and 110 (34%) rated it better, but there was no difference by any of the intervention factors.

113 participants (35%) made positive comments about the booklets and 38 (12%) made negative comments

Patients with personalised booklets were more likely to mention the relevance of the information than those given only general information (41% v 15%; $X^2 = 9.3$, 1df; $P = 0.002$)

Use of the booklets with others:

Compared with patients having general information only, patients with personalised information were more likely to show their booklets to their confidant (85% v 70%; Chi squared = 10.1, 1df; $P = 0.001$), to someone else in the household (32% v 19%; Chi Squared 2 = 6.8, 1df; $P = 0.009$) and to someone outside the household (33% v 22%; Chi squared = 4.3, 1df; $P = 0.04$). There was no difference for the other two intervention factors. Those with personalised information were more likely than those with general information only to think that it helped in discussing their cancer or its treatment (80% v 65%; Chi squared = 4.2, 1df; $P = 0.04$).

Changes in social support:

Patients' social support scores showed a considerable range of changes from baseline to follow-up:

Informational support ranged from - 12 to 12; Emotional support from - 10 to 7; Instrumental support from - 8 to 7 and Negative interactions from - 11 to 22.

There were some unexpected differences by the intervention factors among patients who had shown their booklets to their confidant. The negative interactions scale showed 42% of patients with personalised information deteriorated, compared with only 24% of those with general information only.

Patients who were given anxiety management advice were more likely to have deteriorated on the instrumental support scale than those not given the advice (27% v 13%).

Changes in anxiety and depression:

At follow-up, 145 patients (45%) had improved anxiety scores.

General comments:

This paper was included because the majority of patients in this study were women, 262 (68%) of whom had BC but of grade unknown. The aim of the study was to explore a hypothesis that different methods of selecting and printing information for cancer patients could improve emotional support and wellbeing.

At recruitment, patients were given a questionnaire to complete at home. The results indicated that there was no difference between the intervention groups in terms of anxiety, depression, social support, age, sex, or length of diagnosis.

Of the patients who answered the questions, 326/375 (87%) were satisfied or very satisfied with the cancer information they had already received, 231/373 (62%) had read at least one CancerBACUP booklet. Only 52/382 (14%) had obtained health information themselves from the internet, but 67 (18%) had been given information from the internet by someone else, and 164 (43%) had never used a computer before.

An error in the randomisation envelopes resulted in the misallocation of one patient, with one of the eight groups having 51 patients and another only 49.

Walker and Podbilewicz-Schuller (2005)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United States

Inclusion criteria:

Age over 18 years

Scheduled to be seen at the MDT clinic for treatment evaluation.

Exclusion criteria:

Previous attendance at the participating MDT clinic

Obvious cognitive impairment

Inability to read and write English.

Population:

Number of patients = 79.

Interventions:

Intervention:

A video presentation of 19 minutes duration called A Guide to Your Visit. This was produced for the study by a professional multimedia company and portrayed the typical sequence of events which the patient might experience during their clinic appointment. The patients in the video are shown to be coping with, rather than mastering, their situation as it was believed that this would model manageable levels of stress as normal. Viewers received specific advice about how to make the most of their clinic appointment and are provided with basic questions which they might wish to ask their doctors.

Comparator:

Patients received a two-page description of the events and professional disciplines of the personnel who would be involved in their appointment. The material was based on that used in the video and was intended to briefly summarise the same information but did not include the suggested questions that they might want to ask.

Ten days after their clinic visit patients from both arms of the study received a questionnaire which was to be returned to the clinic.

Outcomes:

Outcomes were self-reported rather than assessed by a professional. The primary outcomes included measures of distress, quality of life (QOL) and secondary outcomes included patient satisfaction, informational preparedness and participation in decision making.

(1) State-Trait Anxiety Inventory (STAI): global measure of state anxiety, apprehension, tension, nervousness and worry. 20-item state section used.

(2) Centre for Epidemiological Studies Depression Scale (CES-D): 20-item self reported measure to assess depressive symptoms

(3) Mini-Mental Adjustment to Cancer scale (Mini-MAC): self-reported questionnaire of 29 items rated on a 4-point Likert scale. 8-point helpless/hopeless subscale only used.

(4) Functional Assessment of Cancer Therapy - General Measures (FACT-G): Quality of life measured with 27 items. This was administered at follow-up.

Distress measures were administered at baseline and follow-up so that baseline emotional distress could be controlled.

Follow-up assessment included a 16-point questionnaire which asked about the clinic

appointment and the intervention. Answers were graded on two 7-point Likert scales.

Follow up:

Baseline data were collected at the authors' institution whilst follow-up data were collected by mail.

6 patients in the intervention arm and 7 patients in the control arm were lost to follow-up. Additionally, 3 patients in the control arm were excluded from analysis because of an allocation error.

Results:

Video group mean age = 52.4 years (SD 8.6)

Pamphlet mean age =58.1 years (SD 10.1)

Authors state the following statistically significant findings:

Unmarried patients in the intervention group (n=13) were less distressed at follow-up than those in the comparator group (n=12) (authors suggest that the video compensated for the lower level of social support available to unmarried patients).

Patients in the intervention group with a history of mental health treatment (n=24) had a better overall QOL than those from the comparator group (n=20) (authors suggest that the video buffers against vulnerability conveyed by having such a history).

Patients of minority status in the intervention group (n=4) had greater overall satisfaction with the clinic appointment compared with those from the comparator group (n=10).

The authors state that the main positive effects of the intervention were: satisfaction with orientation controlling for baseline fatalism (P=0.05), patient information controlling for education (P=0.05) and readiness to ask questions (P=0.05).

There were no significant differences between the two arms in terms of participation in treatment decision-making, satisfaction with the overall MDT appointment.

General comments:

This paper describes a RCT that compared the use of a video presentation with a pamphlet, both of which aim to prepare recently diagnosed breast cancer patients scheduled for evaluation and treatment planning. Authors hypothesised that the intervention might lead the patients to be less distressed, have a higher QOL, have satisfaction with their clinic visit and enjoy greater participation.

Participants were enrolled between July 2000 and January 2002 after being selected from the clinic schedule and approached by a research assistant over the telephone. The preliminary interview took place with the patient one hour before their scheduled clinic appointment at which point their allocation to treatment or comparator group was revealed to them and to the researcher, hence both were un-blinded. Random assignment was based on a computer generated allocation sequence which was developed by the principal investigator.

Patient demographics were self reported and clinical records were used to confirm cancer staging. There were 15/42 patients with stage II-IV breast cancer.

The total patient number was low and the sub-group analyses therefore significantly underpowered to allow the authors' conclusions much validity. Rather, it seems that, with a few exceptions (which in themselves come very close to non-significance) the intervention was ineffective in most respects.

Williams and Schreier (2005)
<p>Design: Randomized controlled trial (therapy), evidence level: 1- Country: United States, setting: Tertiary care</p>
<p>Inclusion criteria: Women aged over 18 years Newly diagnosed with breast cancer Receiving intravenous chemotherapy English speaking Capable of hearing normal conversation Oriented to time, place and person Living in a community setting KPS >70% Not undergoing therapy other than chemotherapy</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 71, age range 30 to 74 years, mean age = 50 years.</p>
<p>Interventions: Intervention (n=38): A 20 minute audiotape consisting of education about exercise and relaxation as means to combat anxiety, fatigue and sleep problems associated with chemotherapy. The transcript was based on prior research studies and written at the (USA) 5th grade educational level to ensure comprehension even amongst those of lower literacy. Patients were instructed to listen to the tape 12-24hours before the start of chemotherapy and as often as desired throughout. The tape was played to patients during their first visit and opportunity was given for discussion about the contents.</p> <p>The audio tape was accompanied by a written self-care diary (SCD) of 3-17 self care behaviours (SCB) composed at the same or a lower educational level.</p> <p>Standard education and care as for the comparator group (see below).</p> <p>Comparator (n=33): Standard education and care given to all chemotherapy patients. Education consisted of verbal instruction of potential side effects given by medical staff at the time of treatment. Patients were also given American Cancer Society literature relating to their treatment.</p>
<p>Outcomes: Side effects: patients were asked how many side effects (fatigue, anxiety and sleep disturbance) they'd experienced and to rate them on a scale from 1 (not severe) to 7 (extremely severe).</p> <p>Average score for the number and efficacy of SCB used.</p> <p>State-Trait Anxiety Scale (STAI): patients were asked to complete this 40 item inventory that measures apprehension, tension, nervousness and worry on a 4-point Likert scale (1 = low anxiety, 4 = high anxiety). For each patient low trait anxiety was classed as a score of 49 or lower and high anxiety as 50 or more.</p>
<p>Follow up: Subjects were interviewed (by the same interviewer) three times by telephone before treatment, 1 month later and after 3 months.</p> <p>1st interview: demographic details obtained, 1st STAI scores (trait and state) calculated, pre-test</p>

on knowledge of SCBs
2nd interview: Completion of 1st SCD and 2nd STAI (state)
3rd interview: Completion of 2nd SCD, 3rd STAI (state) and post-test knowledge of chemotherapy side effects.

Results:

Anxiety:

In both 1st and 2nd SCDs, patients in the control group reported higher anxiety and the severity ratings increased for both groups over time.

Severity of anxiety recorded in the 1st SCD correlated (Pearson's test) with the 2nd STAI and the 2nd SCD correlated with the 3rd STAI.

There was a significant difference in the mean number of SCBs used for anxiety in the 1st SCD - the intervention group reported more SCBs and higher effectiveness for all behaviours. In the 2nd SCD there was no significant difference between the groups in the number of SCBs used for anxiety.

In the 1st SCD more women in the intervention than comparator group reported used the recommended SCBs for anxiety and reported more effectiveness for all the behaviours.

Fatigue:

A higher proportion of women in the intervention than comparator group reported fatigue and the severity rate increased from the 1st to the 2nd SCD for both groups.

In the 1st SCD there was no significant difference between arms in the frequency of the SCBs used for fatigue. Both groups increased the use of exercise, other activities and caffeine intake between the 1st and 2nd SCDs (nsd)

Sleep disturbance:

More women in the control than intervention group reported difficulty in sleeping but the severity increased for both arms from 1st to 2nd SCD.

In the experimental group more patients used the SCB for sleep problems at the 2nd compared with the 1st SCD but reported less effectiveness for all behaviours except 'trying not to think about the side effect'. Symptom severity increased over time for all patients.

There was no significant difference between arms in any side effects: anxiety fatigue or sleep disturbances. Women showed an increase over time in their knowledge of side effects and the basic behaviours to manage them but there was wide variation in compliance with using the intervention. The median rating of usefulness on a 1-10 scale was 8. The most useful items were reported to be information on anxiety, stress, nausea and vomiting, sore mouth and fatigue.

General comments:

This paper describes a RCT which tests an educational audiotape regarding side effects of chemotherapy. This was based on self-care deficit nursing theory (Orem 1995) and a modification of an existing SCD (Nail 1991).

Patients were randomised into two groups but there are no details on blinding allocation or randomisation methodology hence the possibilities of bias exist. Authors stated that there were no significant differences in any baseline demographic variable between the arms.

4/33 patients in the control group and 3/38 in the intervention group had stage III/IV breast cancer. Nearly half of the patients were African-Americans.

Statistical analysis included repeated measures ANOVA for side effects.

Winzelberg <i>et al.</i> (2003)
Design: Randomized controlled trial (therapy), evidence level: 1- Country: United States
Inclusion criteria: Females receiving a diagnosis of breast cancer within previous 32 months No suicidal intent Living in California Being able to communicate in written English
Exclusion criteria: None stated
Population: Number of patients = 72, age range 30 to 69 years, mean age = 50 years.
Interventions: Intervention (n=36): 12-week structured, web-based support group 'Bosom Buddies', moderated by a mental health professional. Each week different subjects were proposed for discussion: (1) introduction (2) getting to know you (information provided on coping with painful emotions) (3) difficult emotions (4) medical team (information provided about how to get more help from physicians, nurses etc) (5) uncertainty and helplessness (information provided about why such feelings arise and strategies for coping) (6) self and body image (7) romance and sexuality (8) family (9) friends (information given about how to seek help from friends and co-workers) (10) fear of recurrence (11) meaning of life (12) closure. Comparator (n=36): Patients were on a waiting list.
Outcomes: To determine if women who participated in an online support group would report improved psychological coping skills and decreased distress when compared with control subjects. Primary measures: (1) Centre for Epidemiological Studies Depression Scale (CES-D): 20-item self reported measure to assess depressive symptoms (cut-off score = 16) (2) Post-Traumatic Stress Disorder Checklist - Civilian version (PCL-C): 17-item self reported measure of PTSD used previously with cancer survivors. Assessed on a 5-point Likert scale of how much each symptom has disturbed the patient. (3) State-Trait Anxiety Scale (STAI): global measure of state anxiety, measuring feelings of apprehension, tension, nervousness and worry rated on a 4-point Likert scale. (4) The Perceived Stress Scale (PSS): 14-item self reported measure of perceived stress during the previous months. Assessed on a 5-point Likert scale. Secondary measures: (1) Cancer Behaviour Inventory (CBI): 51 items on 6 subscales. Perceived ability to implement cognitive behavioural strategies for coping with cancer as a serious illness. (2) Mini-Mental Adjustment to Cancer scale (Mini-MAC): self-reported questionnaire of 29 items rated on a 4-point Likert scale. To assess the specific ways of responding to cancer. Frequently used with breast cancer patients according to the authors. 5 subscales used: fighting spirit, helpless/hopeless, anxious preoccupation, denial and fatalism. Group experience: A 9 item questionnaire designed to assess the intervention i.e. the group experience. Rated on a

4-point Likert scale.
Follow up: N/A
Results: There were no baseline differences between patient characteristics in the two arms on any measure. Effect size [measuring the degree to which the two arms differ where a small effect = 0.1, medium effect = 0.3 and large effect = 0.5. This scale is from -1 (maximum negative effect) to +1 (maximum positive effect) and 0 no effect]: CES-D = 0.54 (P<0.01) PCL-C = 0.45 (P<0.01) STAI = 0.37 (P<0.05) PSS = -0.05 (nsd) CBI (nsd): Seeking support = 0.15 Seeking understanding = 0.11 Coping = 0.04 Affect regulation = 0.07 Positive attitude = -0.28 Activity/independence = 0.13 Mini-MAC (nsd): Helpless/hopeless = 0.08 Anxious preoccupation = 0 Fighting spirit = -0.32 Cognitive avoidance = 0.14 Fatalism = 0.03 All secondary outcomes proved not to be significantly different between the intervention and comparator groups. Patients evaluation of the group experience (proportion reporting 'a lot' or 'great deal'): Getting support and encouragement = 65% Helping others = 56% Learning problems are not unique = 56% Developing new friendships = 63% Getting advice = 55% Expressing true feelings = 65% Modelling self after group participants = 30 Confronting difficult problems and fears = 44 Discussing sexual concerns = 44
General comments: This paper describes a RCT of an internet support group for women with breast cancer. Although the intent and outcomes were mainly psychosocial support, this paper was included because the intervention also provided a means of information provision which participants rated as being of great value. Participants were recruited through public service announcements, newspapers and flyers distributed to oncology offices. The inclusion criteria and demographics were self reported - clinical data were not collected or validated with physicians. The summaries of patient characteristics might therefore be inaccurate. At baseline, a third of patients overall were participating in other breast cancer support groups or individual counselling. It is not stated whether or not these activities continued throughout the 12-

week study and no post-study data were collected on psychological interventions. It might be difficult to determine if the intervention was responsible for the observed results i.e. lacking in internal validity.

Once patients had completed online questionnaires they were randomly assigned to the intervention or to the control group. Since there is no explanation of the process of randomisation there is an obvious possibility of selection bias since the reviewers may have had access to the participants' answers before allocating them to a group. At the end of the 12 weeks patients repeated the questionnaires.

Communication was asynchronous. No medical or psychological interpretations or advice was given by moderators despite the fact that they were appropriately trained. Experienced help was offered in the event of a crisis.

Statistical analysis was very thorough and included testing the baseline differences between intervention and control groups in other words, the effectiveness of the randomisation process, examining the patient demographic in participants who had not completed the questionnaires and comparing the intervention and comparator in terms of outcomes. Intention to treat analysis was performed. Differences between arms were reported in terms of effect size using pre-and post-study data from the questionnaires and a pooled standard deviation.

Authors conclude that the intervention demonstrated effectiveness in reducing patient scores of depression, perceived stress and cancer-related trauma measures with moderate effect size. However, contrary to expectation the intervention made no significant difference in terms of measures of anxiety or in the general or specific aspects of coping with cancer.

This intervention would only be of value to people who own or have access to a computer and, since some of the study participants were lent machines for the purpose, this underlines the fact that this intervention would not be freely available to all breast cancer patients. Additionally, the use of the intervention would require a degree of computer literacy, a condition which was not addressed in this study.

Updated evidence (3.1.2)

Evidence Summary

One RCT (Aranda *et al.*, 2006) compared a breast care nurse-led intervention of support and information compared with a standard care control group. The intervention comprised a face to face talk with the nurse who listened to concerns, assessed need, was empathic and who gave coaching in self-care, stress reduction and communication. Follow-up was by telephone after 1 and 3 months. The authors found that the intervention may have been lacking in intensity since generally QOL had not been improved or perceived need reduced. Sub-group analyses of a low number of patients suggested that women with greater need may have derived a greater benefit from the intervention.

Reference

Aranda S., Schofield P., Weih L., Milne D., Yates P and Faulkner R (2006) Meeting the support and information needs of women with advanced breast cancer: a randomised controlled trial. *Br J Cancer* **95**: 667-673

Evidence table

Question: Effectiveness of information tools
Created by: Karen Francis on 31/07/2008

Aranda <i>et al.</i> (2006)
Design: Randomised controlled trial (therapy). Evidence level: 2 Country: Australia
Inclusion criteria: Women with a new diagnosis of advanced breast cancer or who had recurrent or progressive disease in the previous 12 months Aged ≥ 18 years Sufficient English for study requirements Access to a telephone for follow-up Verbal and written consent
Exclusion criteria: None stated.
Population: Number of patients = 105. Age range: 34 to 85 years. Median ages: 55-57 years
Interventions: Intervention group (n=59): [1] Face to face intervention occurred within 10 days of randomisation and comprised a 1 hour session with a breast care nurse (BCN) in the company of a significant other. The session comprised active listening on behalf of the nurse who offered empathy and support and established the level of patient understanding. Patient needs were identified verbally and from questionnaire responses. Coaching was given in self-care, stress reduction and communication with realistic goals set in these areas. The session was concluded by summarising reviewing and reinforcing key issues, making referrals and arranging follow-up. [2] Information cards were given to the patient. These were concerned with self-care and communication strategies and were evidence based. This material was accompanied by a relaxation CD and a personal care plan relevant to the individual. [3] A written summary of the meeting was provided to the treating physician and entered into the patient's medical record. The BCN telephoned the patient 1 week after the intervention to determine progress and to identify any remaining concerns, reinforce strategies discussed and prompt for new concerns. More information cards were posted to the patient. Again the treating physician was informed of the outcome in detail. Follow-up questionnaires were repeated after 1 and 3 months. Control group (n=46): women received standard care including referral to a breast care nurse or support nurse not connected with the study.
Outcomes: Quality of life (QOL) and perceived needs of the patient (psychological, health, information, physical & daily living, patient care & support and sexuality).
Follow up: On enrolment a baseline questionnaire was completed and was repeated after 1 month and 3 months. This contained items concerning demography, Supportive Care Needs Survey (SCNS) and EORTC QLQ-30 quality of life assessment tool. Other patient data was obtained from medical records. 72/105 women completed the 1 month follow-up (36 in each arm). At this point, 4 women had died and 12 were lost to follow-up. 60/105 women completed the 3 month follow-up (30 in each arm). At this point 5 women had died and 10 were lost to follow-up. The overall response rate

was therefore 71% and 63% for 1 and 3 month follow-up respectively.

The average time taken for the first part of the intervention was 59 minutes. The most common concerns were related to family and treatment. Follow-up telephone calls lasted, on average, for 22 minutes. 36% of women reported using all the strategies suggested during their face to face intervention.

Results:

At baseline, there was no significant difference between study arms in QOL or SCNS data overall or from specific sub-groups. Over time QOL declined slightly overall.

No significant differences were found between the intervention and control groups either from the SCNS data for from EORTC QLQ-30 sub group scores. However, when data were grouped according to need, those women with high baseline needs (baseline scores > 50) gained a significant advantage from the intervention compare with controls when measured by the psychological needs sub-scale of SCNS (P = 0.026) (data not shown).

General comments:

This paper presents the findings from a randomised controlled trial comparing a nurse-led intervention of support and information compared with a standard care control group. 172 women were approached at four treatment centres in Australia and 105 entered the study, the remainder declining to participate.

Patients were randomised by a sealed envelope method after initial baseline data had been collected. The two treatment groups were similar in most respects although the intervention arm had more patients receiving radiotherapy and more women in the control group had young children.

The authors concluded that the intervention may have been lacking in intensity i.e. a higher number of sessions may have had more effect. But generally QOL had not been improved or perceived need reduced. Sub-group analyses of a low number of patients suggested that women with greater need may have derived a greater benefit from the intervention.

Elements of this study do indicate sources of bias. The initial refusal by women with metastatic breast cancer to be involved with this trial was, for some apparently, due to tiredness which suggests that women with a poorer health state were not represented. In addition, this particular study excluded rural and/or non-English speaking women.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Chapter 4 – Systemic Disease-modifying Therapy

4.1 What is the choice of 1st line treatment for patients with metastatic breast cancer, endocrine therapy or chemotherapy?

Short summary

Only one paper was appraised for this topic. A high quality systematic review (Wilcken *et al.*, 2006) examined ten RCTs of chemotherapy vs endocrine therapy, the most recent of which was published in 1995 (even though Cochrane databases were searched as recently as October 2006).

Chemotherapy and endocrine therapy were equal in terms of overall survival but tumour response was variable between studies. No data were presented for quality of life (QOL) or adverse events but, in narrative form, the reviewers stated that in the majority of studies chemotherapy had resulted in higher levels of toxicity (predominantly nausea, vomiting and alopecia) but that it was not clear in which direction QOL had been affected as the results were conflicting.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Individuals with metastatic breast cancer	Any conventional chemotherapy	Any endocrine therapy	<ul style="list-style-type: none"> • Tumour response • Time to progression • Time to treatment failure • Overall survival • Toxicity • QOL

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence statement

Only one paper was appraised for this topic. A high quality systematic review (Wilcken *et al.*, 2006) examined ten RCTs of chemotherapy vs endocrine therapy, the most recent of which was published in 1995 (even though Cochrane databases were searched as recently as October 2006). The definition of chemotherapy included any conventional cytotoxic chemotherapy with or without colony stimulating factors but excluded cytokines, monoclonal antibodies and high-dose chemotherapies requiring stem cell support. Endocrine therapies included anti-oestrogens, oestrogens, androgens, aromatase inhibitors, progestagens and ovarian or adrenal ablations but excluded corticosteroids when given alone.

The analysis for overall survival comprised 692 women and indicated that there was no significant difference between chemotherapy and endocrine therapy (HR = 0.94 (95%CI: 0.79-1.12, P = 0.5).

Survival after one or two years was, similarly, not significantly different between comparators (HR = 1.03 (95%CI: 0.74-1.43) and HR = 0.98 (95%CI: 0.72-1.34) respectively).

In terms of tumour response to treatment (n = 817 patients), statistical analysis appeared to favour endocrine therapy (RR = 1.25 (95%CI: 1.01-1.54, P = 0.04)) but since the two major contributing studies presented findings in opposite directions, the between studies heterogeneity was significant and hence this result should be viewed with caution. However, since the more up-to-date chemotherapeutic and endocrine agents differ from those commonly used at the times when the included studies were published (i.e. pre-1995) these results may not accurately reflect the comparison between modern regimes anyway. It was the reviewers' opinion that this might cause the value of endocrine therapy in improving survival to have been underestimated.

No data were presented for quality of life or adverse events but, in narrative form, the reviewers stated that in the majority of studies chemotherapy had resulted in higher levels of toxicity (predominantly nausea, vomiting and alopecia) but that it was not clear in which direction QOL had been affected as the results were conflicting.

The reviewers concluded that for women with MBC, in whom hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease.

Reference

Wilcken N., Hornbuckle J and Ghersi D (2006) Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database of Systematic Reviews: Reviews.

Evidence table

Question: Endocrine therapy or chemotherapy as first line treatment?

Created by: Karen Francis on 22/05/2007

Wilcken <i>et al.</i> (2006)
Design: Systematic review of RCTs (therapy), evidence level: 1++ Country: Australia
Inclusion criteria: Included studies: Properly randomised (defined) controlled trials comparing chemotherapy with endocrine therapy Included patients: Women with MBC (not disease recurrence alone)
Exclusion criteria: None stated
Population: -
Interventions: Chemotherapies Included: Conventional cytotoxic chemotherapy with or without colony stimulating factors Excluded: cytokines, monoclonal antibodies, high-dose chemotherapies requiring stem cell support. Endocrine therapies Included: anti-oestrogens, oestrogens, androgens, aromatase inhibitors, progestagens, ovarian

or adrenal ablations Excluded: corticosteroids given alone
Outcomes: Primary: Overall survival (OS) Secondary: Tumour response rate, quality of life (QOL), toxicity.
Follow up: NA
Results: Overall survival (n = 692): When all studies were included HR = 0.94 (95%CI: 0.79-1.12, P= 0.5). There was no significant difference between chemotherapy and endocrine therapy. The P value for between studies heterogeneity was 0.05. When one trial was excluded, because it was not clear if all patients had MBC, the analysis then favoured endocrine therapy but did not reach significance: HR = 0.84 (95%CI: 0.70-1.02, P = 0.08). There was no significant difference between endocrine and chemotherapy in survival after 1 or 2 years: after 1 year HR = 1.03 (95%CI: 0.74-1.43) and after 2 years HR=0.98 (95%CI: 0.72-1.34). Tumour response (n = 817): A pooled estimate of reported response rates showed a significant advantage for chemotherapy: RR = 1.25 (95%CI: 1.01-1.54, P = 0.04) but between studies heterogeneity was significant (P = 0.0009) and the two largest trials showed trends in opposite directions. Toxicity and QOL The review included no data on these outcomes but summarised findings in narrative form. The reviewers reported that there was little in the way of information but that 6/7 trials mentioned increased toxicity with chemotherapy (nausea, vomiting and alopecia). 3/7 trials mentioned QOL and differed in their conclusion since one favoured chemotherapy, one endocrine therapy and one finding no difference between them.
General comments: This was a good quality Cochrane review of chemotherapy alone versus endocrine therapy for MBC. The literature search identified ten suitable RCTs, most of which were dated (1963-1995) and of low patient number (n = 50-226). The reader was referred to the Cochrane Breast Group search methodology which is generally used in such reviews and is acknowledged to be thorough and comprehensive. Papers for inclusion were selected independently by two expert reviewers and quality assessment of each study was undertaken by a third reviewer. Hazard ratios and confidence intervals were constructed at 3 monthly intervals, either with data taken from the published survival curves or obtained indirectly using established methods from available summary statistics. Other data were extracted independently by the two reviewers and a meta-analysis was undertaken. Planned sub-group analyses of prognostic factors were abandoned due to the insufficient numbers of trials of adequate size. The available evidence suggested that treating first with endocrine therapy (when receptors are present) is associated with an inferior tumour response, similar overall survival, less toxicity and an uncertain effect on QOL. However, since many trial participants were either hormone unresponsive or were not tested the advantage of endocrine therapy may have been underestimated.

The observed between-studies heterogeneity may have resulted from an uneven number of trial participants being hormone responsive but this was speculative.

Since the more up-to-date chemotherapeutic and endocrine agents differ from those commonly used at the times when the included studies were published, the results may not accurately reflect the comparison between modern regimes. It is the reviewers' opinion that this might further underestimate the value of endocrine therapy in improving survival.

The reviewers concluded that for women with MBC, in whom hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease.

There were no known conflicts of interest.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

4.2 What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer?

4.2.1 Women with metastatic breast cancer

Short summary

The evidence base for this question comprises one guideline (Eisen *et al.*, 2004), four systematic reviews (Mauri *et al.*, 2006; Gibson *et al.*, 2007; Ferretti *et al.*, 2006 and Crump *et al.*, 1997), three RCTs (Chia *et al.* 2008, Mouridsen *et al.* 2007 and Goss *et al.* 2007) and a small, low quality comparative study (Catania *et al.* 2007). The number of study participants exceeded 30,500 women, the majority of whom were post-menopausal with metastatic breast cancer. Most of the papers were of high quality, although the guideline did review non-published abstracts.

Pre-menopausal women with metastatic breast cancer experienced no significant difference in tumour response or survival between ovarian ablation and tamoxifen as first line therapy. Atamestane and toremifene as first line combination therapy resulted in similar tumour response and survival compared with letrozole alone.

Fulvestrant and exemestane showed equivalent efficacy for women that had previously received non-steroidal AIs for the treatment of advanced breast cancer. However, the lack of a placebo comparator meant that it was not possible to assess the true clinical activity of either agent. Limited evidence also suggested that fulvestrant conferred short term benefit to heavily pre-treated women with metastatic disease by postponing the requirement for chemotherapy.

Good evidence showed that there was significant clinical benefit, increased progression-free survival and ~13% reduction in the risk of death with third generation AIs compared with standard endocrine therapy (the analyses included all treatment lines). No individual AI was better than another in this regard. Very limited evidence suggested that there was no significant difference between the AIs and standard therapy in patient reported quality of life. However, more gastrointestinal symptoms and hot flushes were associated with AI therapy compared to standard endocrine therapy but were fewer reports of blood clots and vaginal bleeding.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Women with metastatic breast cancer	<ul style="list-style-type: none"> • Aromatase inhibitors • Fulvestrant • Tamoxifen • Progestagens • Stilboestrol • Testosterone • Ovarian ablation 	Each with each other	<ul style="list-style-type: none"> • Time to progression • Overall survival • Toxicity • QOL • Response rate

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

The evidence base for this question comprises one guideline and four systematic reviews. The total number of participants exceeds 28,000 and the majority of women were post-menopausal and with metastatic breast cancer. Only the review examining the issue of ovarian ablation versus tamoxifen included patients who were pre-menopausal. All the reviews were of good quality.

Mauri *et al.* (2006) presented a high quality systematic review of 23 RCTs in which a total of 8,503 women participated. These women were described as having advanced breast cancer (locally advanced, recurrent or metastatic disease). There were no inclusion/exclusion criteria regarding existing endocrine or menopausal status. The included studies compared all generations of aromatase inhibitors (aminoglutethimide, formestane, fadrozole, vorozole, letrozole, exemestane and anastrozole) with other endocrine therapies (tamoxifen, megestrol acetate and medroxyprogesterone acetate).

The only data used in the meta-analysis related to overall survival and the results were presented for each generation of aromatase inhibitor. This approach revealed that only the third generation AIs provided a statistically significant survival benefit (HR = 0.87 (95%CI: 0.82-0.93) P<0.001) and reduced mortality (HR = 0.91 (95%CI: 0.86-0.96) P = 0.001) when compared with standard endocrine therapy. The authors concluded that even in first line treatment of MBC this group of AIs might be preferable to tamoxifen.

This was a thorough, high standard analysis but which may have invited an element of bias by excluding all but published, peer reviewed papers and by not formally scoring included studies for quality. Whilst this may have led to an overestimation of benefit in favour of the intervention, the lack of detail about intention-to-treat and cross-over effects within the included trials may conceal a dilution of such benefit so that it would be hard to say that, if bias existed, it would favour the intervention or comparator.

Another very good quality systematic (Cochrane) review (Gibson *et al*, 2007) analysed data from 30 RCTs in which 10,054 women participated. The patient group included only post-menopausal women with advanced or metastatic breast cancer but excluded those who only had locally advanced disease. Aromatase inhibitors (aminoglutethimide, formestane, anastrozole, exemestane, fadrozole, letrozole and vorozole) were matched against megestrol acetate, tamoxifen, fulvestrant, medroxyprogesterone acetate and hydrocortisone. The primary outcome

was overall survival. Secondary outcomes of interest included progression-free survival, clinical benefit, tumour response and adverse events.

When all aromatase inhibitors were included in the analysis, there were no significant benefits compared with standard endocrine therapy but when third generation AIs were analysed separately there was a significant survival benefit (HR = 0.88 (95%CI: 0.88-0.96)) which was strikingly similar to the result obtained by Mauri *et al.* (2006). However, progression-free survival was not significantly enhanced by the third generation AIs, with the exception of exemestane. The authors noted a high level of heterogeneity between the included studies which may make this conclusion unsafe. Similarly the heterogeneity between studies with regard to tumour response data may disqualify the apparent significant advantages in clinical benefit seen with AIs (OR = 0.78 (95%CI: 0.63-0.96)) or tumour response (OR = 0.77 (95%CI: 0.62-0.96)).

Adverse events were thoroughly analysed and reported but, once again, the findings were confounded with significant heterogeneity between studies such that the results would have to be regarded with caution. Generally, use of AIs was associated with higher incidences of nausea, vomiting, and hot flushes compared with megestrol acetate and of diarrhoea and rash when compared with tamoxifen, but fewer incidences of thromboembolic events and vaginal bleeding, depending on the particular comparator. The authors conclude that there is a considerable survival advantage, particularly with the more modern AIs compared with standard endocrine therapies. Unfortunately, between-studies heterogeneity does interfere with the interpretation of significant findings in favour of AIs for all outcomes but overall survival.

Ferretti *et al.* (2006) presented a systematic review of 7 trials (2,787 participants) which had compared AIs against standard endocrine therapy. The data analyses were by sub-group: non-steroidal AIs (fadrozole, letrozole, anastrozole and vorozole); all AIs (as preceding group plus formestane and exemestane) and third generation AIs only. The primary outcomes were tumour response rate and time to progression with secondary outcomes of overall survival and clinical benefit.

Unlike the systematic reviews by Mauri *et al.* (2006) and Gibson *et al.* (2007) the results of this analysis suggested that there was no significant survival benefit in treatment with AIs with regard to overall survival however the methodology employed to produce this result was different. Rather than selecting median survival times and using these to extrapolate the efficacy of intervention against comparator, Ferretti *et al.* (2006) extracted the proportion of patients surviving at a single (6 month) time point and combined these data from included studies. The result is therefore only relevant at that time point and does not inform about the efficacy of the intervention on survival overall. This methodology was also used to assess the time to progression but significant heterogeneity between the included studies negated the findings of this outcome, together with those for tumour response and clinical benefit. The analyses showed that third generation AIs conferred a significant benefit compared with standard endocrine therapy with regard to TTP and clinical benefit whether analysed using fixed- or random-effects models but that between-studies heterogeneity is still significant.

A systematic review by Crump *et al.* (1997) examined a comparison of tumour response and survival between ovarian ablation (surgical or by radiation) and tamoxifen for the first line treatment of metastatic breast cancer in pre-menopausal women. There were four included studies with a total of 220 participants. The meta-analysis was well prepared and the reviewers followed up participants and contacted study authors with the aim of data completion (by the time of their analysis there were ten survivors). The data collection and meta-analysis were thorough but the review itself was less than optimally systematic with little of the methodology explained. All study participants had estrogen +ve (or unknown) tumour status and were pre-menopausal with previously untreated metastatic disease.

There was a deliberate cross-over design of included studies in order to investigate whether the response to the first treatment would prove a prognostic factor, predicting the response to the other treatment administered following disease progression. Whilst there was no significant difference in tumour response, disease progression or survival between ovarian ablation and tamoxifen as first line therapies, the response to either of them was found to predict the subsequent response to the other. With this in mind the authors felt that there was no evidence to suggest that irreversible ovarian ablation, with attendant side effects, would be suitable as first line therapy but that the prior response to tamoxifen might predict its suitability as second line treatment.

The Cancer Care Ontario practice guideline 'The role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer' was constructed around a high quality systematic review (Eisen *et al.*, 2004). The patients and settings included in the trials were diverse and not reported in detail. The patient group included was specified as postmenopausal women with stage IV (metastatic) breast cancer. Abstract data were included in the meta-analysis of first line treatment, caution must be taken when considering this evidence because abstract evidence can be limited and left to interpretation by the reviewer.

- There were 3 RCTs comparing anastrozole with tamoxifen, one of letrozole versus tamoxifen and 1 of exemestane versus tamoxifen as first-line therapy for metastatic breast cancer. Treatment with selective aromatase inhibitors was associated with higher objective response rates and prolonged time to progression compared to tamoxifen, but definitive survival and quality-of-life data were not available. The toxicity profile of the aromatase inhibitors was acceptable.
- There were 3 RCTs comparing letrozole to megestrol acetate or aminoglutethimide, 2 of anastrozole versus megestrol acetate, and 1 of exemestane versus megestrol acetate as second-line hormonal therapy for metastatic breast cancer. Women eligible for these trials included those who relapsed during or were within 6 months of completion of adjuvant anti-estrogen therapy and those who progressed on first-line anti-estrogen therapy for metastatic disease. Treatment with selective aromatase inhibitors was associated with equivalent or better objective response rates and time to progression, and a superior toxicity profile, compared to megestrol acetate or aminoglutethimide. Two individual trials and a meta-analysis of individual-patient data from four trials detected a modest but statistically significant survival advantage for aromatase inhibitors, compared to control. There were no consistent differences in measures of quality of life between aromatase inhibitors and control therapy in randomized trials. There were no significant differences between doses of anastrozole of 1.0 and 10 mg, but two of three trials detected significantly higher survival rates with letrozole 2.5 mg compared to 0.5 mg.
- A non-blinded RCT of letrozole versus anastrozole (abstract only) detected a statistically significant increase in response rate with letrozole compared to anastrozole as second-line treatment but no difference in time to progression. No survival or quality-of-life data are available from this trial.
- Data from three phase II trials indicate that exemestane therapy, as third- or greater-line hormonal therapy, was associated with modest but appreciable rates of objective response and is well tolerated. There are no data from clinical trials of other aromatase inhibitors in this setting.

References

Crump M., Sawka CA., DeBoer G., Buchanan RB., Ingle JN., Forbes J., Meakin JW., Shelley W and Pritchard KI (1997) An individual patient-based meta-analysis of tamoxifen versus ovarian ablation as first line endocrine therapy for premenopausal women with metastatic breast cancer (DARE structured abstract). *Breast Cancer Res Treat* **44**: 201-210.

Eisen A., Pritchard K., Johnston M and Oliver T (2004) Role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. *Curr Oncol* **11 (2)**: 41-52.

Ferretti G., Bria E., Giannarelli D., Felici A., Papaldo P., Fabi A., Di CS., Ruggeri EM., Milella M., Ciccamese M., Cecere FL., Gelibter A., Nuzzo C., Cognetti F., Terzoli E and Carlini P (2006) Second- and third-generation aromatase inhibitors as first-line endocrine therapy in postmenopausal metastatic breast cancer patients: a pooled analysis of the randomised trials. *Br J Cancer* **94 (12)**: 1789-1796.

Gibson LJ., Dawson CL., Lawrence DJ and Bliss JM (2007) Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database of Systematic Reviews: Reviews Cochrane Database of Systematic Reviews 2007 Issue 1. Chichester (UK): John Wiley & Sons, Ltd.

Mauri D., Pavlidis N., Polyzos NP and Ioannidis JP (2006) Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst* **98 (18)**: 1285-1291.

Evidence tables

Question: What is the most effective hormone treatment for women with metastatic breast cancer?

Created by: Karen Francis on 27/06/2007

Crump <i>et al.</i> (1997)
Design: Systematic review of RCTs (therapy), evidence level: 1- Country: Canada (federal state, Commonwealth Realm)
Inclusion criteria: Studies: RCTs (both published and unpublished) comparing ovarian ablation with tamoxifen Patients: ER +ve status or unknown Premenopausal (experiencing regular menstruation or if last period was within 6-12 months of study entry) Women with a hysterectomy but under 50 years acceptable Measurable disease No prior therapy for MBC
Exclusion criteria: None stated
Population: Number of patients = 220
Interventions: 1] Tamoxifen at either 20 or 40mg per day (n = 109) 2] Ovarian ablation by oophorectomy or radiation (n = 111)
Outcomes: Tumour response (complete response CR, partial response PR, stable disease SD, disease progression PD); Survival
Follow up: Response evaluation occurred at 2-3 months after the start of therapy. At the time of the analysis 210 patients had died (105 in each group).

Results:

Initial treatment response:

There was no significant difference in the response rate due to treatment across the trials ($P = 0.94$) even when only assessable patients were included ($P = 0.88$)

Reduction in the odds of disease progression in favour of tamoxifen compared with oophorectomy as first line therapy was $14 \pm 12\%$ $P = 0.32$ (nsd)

Reduction in the odds of mortality in favour of tamoxifen compared with oophorectomy as first line therapy was $6\% \pm 13\%$ $P = 0.71$ (nsd)

Cross-over treatment:

54/111 oophorectomy patients received tamoxifen on progression. 34/109 tamoxifen patients underwent oophorectomy ($P = 0.009$).

Tumour response of 47/54 oophorectomy patients receiving tamoxifen as second line therapy that could be evaluated:

0 CR + 4 PR + 16 SD + 27 PD

Tumour response of 25/34 tamoxifen patients receiving oophorectomy as second line therapy that could be evaluated:

1 CR + 5 PR + 9 SD + 10 PD

Data for the 47 evaluable ovarian ablation patients who crossed over to tamoxifen showed a significant association with regard to response status between first and second line treatment (Spearman rank coefficient = 0.398; $0.02 < P < 0.05$). 1/15 patients who initially responded to ovarian ablation responded to tamoxifen. 3/32 patients failed to respond to ovarian ablation but responded to tamoxifen.

Data for the 25 evaluable tamoxifen patients crossing over to ovarian ablation also showed a significant association with regard to response status between first and second line treatment (Spearman rank coefficient = 0.332; $0.02 < P < 0.05$). 3/9 patients who initially responded to tamoxifen also responded to ovarian ablation. 3/16 patients failed to respond to tamoxifen but responded to ovarian ablation.

General comments:

This paper presents a meta-analysis of 4 RCTs reporting on the comparison between ovarian ablation (by surgery or RT) vs tamoxifen as first line endocrine therapy for MBC in premenopausal women.

All studies purposely had a crossover design in order to detect any effect of the first therapy on the response to the second at the time of disease progression. All data was stated to have been analysed on an intention to treat basis.

Individual patient data was obtained from the principal investigators of each study, not just abstracted from the published work. Patient follow-up was also updated. This is rigorous preparation for a meta-analysis.

RCTs were identified through Medline and CancerLit databases and by hand-searching related publications and texts. Authors of unpublished trials were contacted with regard to the inclusion of data.

Appropriate statistics were employed to define the comparison of response rates and overall survival between the two patient treatment groups.

The number of patients overall is quite low but the analysis is thorough and of statistical value. Authors conclude that there is no evidence to support the use of ovarian ablation given to premenopausal women in favour of tamoxifen. Further, the response to tamoxifen predicted the response to ablation and therefore whether or not this irreversible treatment would be of advantage as a second line treatment at disease progression.

The drawbacks to this study were that the review of literature was rather non-systematic with little methodology reported with regard to selection criteria, reviewing, search terms etc. However the meta-analysis itself appeared to be thorough. The conclusions should be viewed cautiously in light of the shortcomings.

Mauri D *et al.* (2006)

Design: Systematic review of RCTs (therapy), evidence level: 1+

Country: Greece

Inclusion criteria:

Studies: RCTs comparing an aromatase inhibitor (AI) or inactivator with tamoxifen or a progestagen. The use of concomitant treatment (e.g. RT) was acceptable providing there was no difference in the numbers of such people treated between intervention and comparator arms. With studies that were reported severally, only the paper with the longest follow-up time (hence the greater number of events) was retained and others were excluded to prevent duplication.

Patients: Women with advanced breast cancer (metastatic or inoperable locally advanced or recurrent breast adenocarcinoma).

Exclusion criteria:

Studies randomising patients with less than stage IV BC
 Patients who had breast malignancies other than adenocarcinoma.
 Meeting abstracts (because they are not peer reviewed)
 Dose escalation studies
 Single arm studies
 Non-randomised or pseudorandomised trials.

Population:

Number of patients = 8504.

Interventions:

1st generation AI: aminoglutethimide (6 studies)
 2nd generation AI: formestane and fadrozole (7 studies)
 3rd generation AI or aromatase inactivators: vorozole, letrozole, exemestane and anastrozole (12 studies)

Comparators:

1st line: tamoxifen (9 studies)
 2nd or subsequent line: progestagens (i.e. megestrol acetate and medroxyprogesterone acetate) (16 studies).

Outcomes:

Overall survival (OS)

Follow up:

N/A

Results:

23 trials were included in the meta-analysis: 4,559 patients were randomised to receive AIs (or aromatase inactivators) and 3,945 patients received standard endocrine therapy.

The median ages of the trial participants across all studies were between 57 and 68 years and all but one of the patients was female, the majority of whom were post-menopausal.

11 trials were double blind; 16 papers described the methods of randomisation; 15 papers described the method of allocation concealment and 18 papers reported sufficient detail of patient withdrawals.

Only 3rd generation AI (or aromatase inactivators) provided a statistically significant survival benefit compared with standard endocrine therapies with OS HR = 0.87 (95%CI: 0.82-0.93) P < 0.001. A combination of data across all RCTs also showed a statistically significant summary effect for mortality with a HR = 0.91 (95%CI: 0.86 - 0.96) P=0.001

The survival benefit for 3rd generation AIs was similar in first line trials whether compared with tamoxifen: harm reduction = 11% (95% CI: 1-19%) P = 0.03 or progestagens (harm reduction = 14% (95%CI: 6-21% P < 0.001

There was no significant between-study heterogeneity (Q = 22.8 with 24 df). This Q value would generate an I² statistic of 5% meaning that only 5% of the total variability in this set of effect sizes was due to true heterogeneity as opposed to sampling error.

1st and 2nd generation AIs gave no significant survival advantages over other endocrine therapies regardless of agent, comparator or treatment line.

General comments:

This paper presents a meta-analysis of 23 studies each of which compares aromatase inhibitors or inactivators against the standard endocrine therapy (either tamoxifen or progestagens). By extracting appropriate Cox proportional hazards data (or estimating the same from log rank test data) from these studies a combined hazard ratio was calculated with respect to overall survival. Appropriate testing for between-study heterogeneity did not identify any significant differences thus supporting the validity of data combining. Data was stratified according to the generation of AI (see 'interventions') and also analysed in sub-groups according to the particular agents and comparisons.

This was a high quality systematic review with only a few negative points: the authors did not present a formal scoring for included studies (i.e. Jadad) although they appear to have been rigorously examined in all respects. Only published papers were included in the analysis which could introduce bias towards a positive result for the intervention.

Authors concluded that the newer aromatase inhibitors show a survival advantage over standard endocrine agents, such as tamoxifen, even for first line treatment.

The prevalence of intention-to-treat analyses and cross-over events in the included studies is not examined - many patients on older type treatments may have been crossed over onto third generation AIs which, had that happened, could have diluted the apparent benefit for those patients who had been randomised to AI initially.

Gibson *et al.* (2007)

Design: Systematic review of RCTs (therapy), evidence level: 1++

Country: United Kingdom

Inclusion criteria:

Included studies:

RCTs of patients with advanced or MBC or RCTs with results stratified by stage of disease such that it was possible to obtain data for those patients.

<p>Included patients: Postmenopausal women with advanced or metastatic breast cancer (at any site) at diagnosis or at relapse.</p>
<p>Exclusion criteria: Excluded studies: Non-English papers, non-systematic reviews, non-randomised studies, conference proceedings without published data (with 1 exception)</p> <p>Excluded patients: Those with local recurrence of breast cancer only Those with positive or unknown endocrine status</p>
<p>Population: Number of patients = 10,054</p>
<p>Interventions: Aromatase inhibitors (AI) vs any other endocrine therapy AI vs no treatment AI plus endocrine therapy vs other endocrine therapy alone Direct comparison between AIs</p> <p>AIs included (no of trials/n): 1st generation: Aminoglutethimide (n = 7)</p> <p>2nd generation: Formestane (n = 2)</p> <p>3rd generation: Anastrozole (n = 4), exemestane (n = 2), fadrozole (n = 6), letrozole (n = 4), vorozole (n = 1) (3rd generation).</p> <p>Comparators: Megestrol acetate (MA), tamoxifen, fulvestrant, medroxyprogesterone acetate (MPA), hydrocortisone (HC).</p>
<p>Outcomes: Primary: Overall survival (OS)</p> <p>Secondary: Progression free survival (from randomisation to progression - PFS); Objective response (complete + partial response - OR); Clinical benefit (objective response + stable disease for >24 weeks - CB); Adverse events (where comparable: nausea, diarrhoea, rash, arthralgia, hot flushes, vaginal bleeding and thromboembolic events).</p>
<p>Follow up: Total number of study participants lost to follow-up, refusals or withdrawals = 51 (these data not included in all studies and therefore this represents a minimum figure).</p>
<p>Results: OS (12 trials n = 4548): The pooled HR = 0.89 (95%CI: 0.82-0.96) a statistically significant (P = 0.003) 11% benefit of treatment with AI with consistent effect across all sub-groups.</p> <p>PFS (10 trials n = 5355): The pooled HR = 0.97 (95%CI: 0.83-1.14) showed that there was no significant effect of AIs on PFS but the result is difficult to interpret due to the significant heterogeneity between AI type and within each AI group. Exemestane was significantly better than a non-AI but vorozole was significantly worse. For anastrozole and letrozole there was significant heterogeneity across studies which precluded finding any significant difference between these AIs and other therapy.</p>

CB (7 studies n = 7594):

Data for 2 studies showed no superiority for AIs against standard endocrine therapy (P = 0.09) but there was significant heterogeneity between studies (P = 0.004).

OR (25 studies n = 7919):

The pooled OR suggests no significant effect of treatment (with aminoglutethimide, formestane, anastrozole, exemestane, fadrozole, letrozole, vorozole) (P = 0.09) again confounded by a statistically significant heterogeneity between studies (P = 0.02). Only letrozole when assessed individually (n=1637) showed a significant benefit over a non-AI (OR = 0.65 (95%CI: 0.51-0.82)).

Sub-group analyses (matching 3rd generation AIs against standard therapy):

There are no data on OS for individual AIs but the AIs in current use (2006) were collectively statistically significantly superior to non-AIs (HR = 0.88 (95%CI: 0.80-0.96)). This was measured in 6 trials. Similarly in 6 trials, PFS was shown to not to be statistically significantly superior for AIs compared with non-AIs (HR = 0.92 (95%CI: 0.75-1.13)) although this was not true for exemestane when tested individually. However there was highly significant heterogeneity in the pooled data and within the other trials (both P < 0.00001). A pooled OR suggests a significant advantage in CB for AIs (OR = 0.78 (95%CI: 0.63-0.96)) but, again, with significant heterogeneity among the trials (P = 0.002). There was a significant advantage of AI therapy with regard to tumour response (OR = 0.77 (95%CI: 0.62-0.96)) but with significant heterogeneity among the exemestane trials.

Adverse events (22 trials, all comparisons):

Hot flushes (18 studies n = 7059):

AI were associated with a statistically significant risk of hot flushes compared with MA (OR = 1.77 (95%CI: 1.42-2.20)) but not with MPA (OR = 0.20 (95%CI: 0.06-0.73))

Nausea (15 studies n = 6602):

AI were associated with a statistically significant risk of nausea compared with MA (OR = 1.84 (95%CI: 1.37-2.47)) but not with tamoxifen (P = 0.32) or fulvestrant (P = 0.81)

Vomiting (2 studies n = 4404):

AI were associated with a statistically significant risk of vomiting when compared with MA (OR = 2.03 (95%CI: 1.42-2.90))

Diarrhoea (9 studies n = 4507):

AI were associated with a statistically significant risk of diarrhoea compared with tamoxifen (OR = 1.64 (95%CI: 1.06-2.13)) but not fulvestrant (P = 0.19)

Rash (12 studies n = 3822):

AI were associated with a statistically significant risk of rash when compared with tamoxifen (OR = 33.61 (95%CI: 4.71-239.97)) and in one trial against MPS (OR = 111.71 (95%CI: 6.75-1849.91)) but not against MA or fulvestrant. However, in the trial of the former there was significant heterogeneity (P = 0.0005)

Vaginal bleeding (4 studies n = 2150):

AI were associated with a statistically significant benefit compared with MA (OR = 0.29 (95%CI: 0.13-0.65)) and, in one trial, against MPA (OR = 0.10 (95%CI: 0.01-0.77)). There was no significant benefit when compared with tamoxifen (P = 0.15)

Thromboembolic events (6 studies n = 2937):

AIs had a statistically significant advantage over tamoxifen (OR = 0.48 (95%CI: 0.27-0.85)) only.

Arthralgia (2 studies n = 2470):

There was no significant difference between AIs and comparators (tamoxifen or MA).

For other adverse events sub-group analysis please see:
<http://www.cochrane.org/reviews/en/ab003370.html>

General comments:

This is a (Cochrane) systematic review of 30 RCTs which compared aromatase inhibitors with other endocrine therapy for the treatment of advanced breast cancer in postmenopausal women.

This is a high quality review and was conducted in a very rigorous manner. Several relevant databases were searched, inclusion criteria were clearly defined (for selection of studies), data extraction was described and the methodological evaluation of included studies was well conducted and reported.

All data were analysed by the reviewers on an intention-to treat basis which may therefore underestimate the treatment effect. The data in many studies were reported (for response) on assessable patients only but this was shown not to be statistically significant when compared with the results from the ITT analysis.

Quality of life outcomes were not reported in this review - this was due to the heterogeneity between included studies that precluded combining the data.

Although over 10,000 women were randomised in these 30 trials, time-to-event data were only available for about half of them and the authors caution to bear this in mind when interpreting the results of the meta-analysis.

It is apparent that the significant heterogeneity between and within studies precluded certainty about interpreting results of many of these comparisons, particularly tumour response and PFS.

The positive effect of AIs on tumour response were apparent against first-line tamoxifen but not other comparators or when compared as second-line treatment. In terms of PFS, treatment with AIs significantly reduced the hazard at first-line only.

The authors conclude that there was a significant survival advantage to AIs, particularly those in current use (anastrozole, exemestane and letrozole) even though only data on half the trial participants were available.

Ferretti *et al.* (2006)

Design: Systematic review of RCTs (therapy), evidence level: 1-
Country: Italy

Inclusion criteria:

Studies: Phase III RCTs comparing AIs with tamoxifen as 1st line therapy for MBC and published as original papers in peer-reviewed journals (there was one exception to this - an abstract of a large RCT presented at the 2004 ASCO conference).

Patients: Postmenopausal women with MBC relapsing on adjuvant therapy.

Exclusion criteria:

Phase II, non-randomised studies, articles or letters

Population:

Number of patients = 2787

Interventions:

Analysis by the following sub-groups. All AIs were compared with tamoxifen as first line therapy

for MBC:

Group AI: included non-steroidal AI (nsAI): fadrozole, letrozole, anastrozole and vorozole and steroidal AI: formestane and exemestane. Excluded the abstract of Paridaens *et al* (see tgAI below)

Group nsAI: included only fadrozole, letrozole, anastrozole and vorozole

Group tgAI: all third generation AIs (including an abstract excluded from other analyses which made a comparison between exemestane and TAM n = 371)

Outcomes:

Primary outcomes: overall response rate (ORR - complete response + partial response), time to progression (TTP)

Secondary outcomes: overall survival (OS), clinical benefit (CB - defined as either CR, PR or stable disease for > 6 months).

Toxicity.

Follow up:

Median follow-up across all trials ranged from 5.1-36 months.

Results:

7 trials were included in the meta-analysis: 1,615 patients were randomised to receive AIs and 1,623 patients received tamoxifen (TAM).

TTP in the AI patients ranged from 7.1-18 months

TTP in the TAM patients ranged from 5.6-9.8 months

OS in the AI patients ranged from 17.4-39.2 months

OS in the TAM patients ranged from 16-40 months

CB in the AI patients ranged from 50-83%

CB in the TAM patients ranged from 38-75.7%

Meta analysis by sub group:

Group AI - fixed effects model:

ORR (n = 2787): RR = 1.13 (95%CI: 1.0-1.28) P = 0.042 (AI)

TTP (n = 2549): RR = 0.88 (95%CI: 0.8-0.96) P = 0.007 (AI)

CB (n = 2787): RR = 1.11 (95%CI: 1.04-1.19) P = 0.001 (AI)

OS (n = 2787): RR = 0.97 (95%CI: 0.79-1.18) nsd

Group AI - random effects model:

ORR (n = 2787): RR = 1.11 (95%CI: 0.89-1.37) nsd

TTP (n = 2549): RR = 0.92 (95%CI: 0.68-1.26) nsd

CB (n = 2787): RR = 1.13 (95%CI: 0.96-1.33) nsd

Group AI - between studies heterogeneity:

ORR: P = 0.03

TTP: P < 0.0001

CB: P < 0.0001

OS: nsd

The significant effect of (steroidal and non-steroidal) AIs on ORR, TTP and CB seen in the fixed effects model are not confirmed in the random effects model but OS is nsd both models.

Group nsAI - fixed effects model:

ORR (n = 2166): RR = 1.23 (95%CI: 1.07-1.42) P = 0.003 (AI)
TTP (n = 1928): RR = 0.77 (95%CI: 0.69-0.86) P < 0.0001 (AI)
CB (n = 2166): RR = 1.21 (95%CI: 1.12-1.31) P < 0.0001 (AI)
OS (n = 2166): RR = 0.94 (95%CI: 0.75-1.78) nsd

Group nsAI - random effects model:

TTP (n = 1928): RR = 1.25 (95%CI: 1.12-1.31) nsd
CB (n = 2166): RR = 1.13 (95%CI: 0.96-1.33) P = 0.018

Group nsAI - between studies heterogeneity:

ORR: nsd
TTP: P = 0.002
CB: P = 0.005
OS: nsd

Only the significant positive effect of non-steroidal AIs on TTP was confirmed between fixed and random effects models.

Group tgAI - fixed effects model:

ORR (n = 2537): RR = 1.28 (95%CI: 1.13-1.44) P < 0.0001 (AI)
TTP (n = 2299): RR = 0.76 (95%CI: 0.69-0.84) P < 0.0001 (AI)
CB (n = 2537): RR = 1.23 (95%CI: 1.14-1.32) P < 0.0001 (AI)
OS (n = 2537): RR = 0.93 (95%CI: 0.76-1.15) nsd

Group tgAI - random effects model:

TTP (n = 2299): RR = 0.74 (95%CI: 0.58-0.94) P = 0.015
CB (n = 2537): RR = 1.26 (95%CI: 1.09-1.46) P = 0.0002

Group tgAI - between studies heterogeneity:

ORR: nsd
TTP: P = 0.004
CB: P = 0.008
OS: nsd

The significant positive effect of third generation AIs on TTP and CB was confirmed between fixed and random effects models. Significance was maintained despite between-study heterogeneity. OS was still not significantly different between AI and TAM patients.

Toxicity:

The incidences of thromboembolic events and vaginal bleeding were significantly less with AI therapy than TAM in all three sub-groups analyses. All studies were non-significant for between-studies heterogeneity for these parameters.

General comments:

This paper described a meta-analysis of seven RCTs (including one abstract) which compared AIs with tamoxifen as a first line therapy for MBC. Both fixed and random effects models were applied to the data which was analysed in sub-groups according to the AI type.

The between-study heterogeneity rendered some of the efficacy results non-significant even though the relative risk results appeared to suggest otherwise. The Q and I squared figures are not given so it is not possible to state the degree of heterogeneity other than as a P value.

Median survival and progression values were not extracted from the included studies but OS and TTP were estimated (probably from Kaplan-Meier curves) at 6 months and these values were used in the meta-analyses. This must be kept in mind when comparing the results of this review with those of other similar reviews that have reported survival outcomes using median values. For example, in the review by Mauri *et al.* (2006) the median OS values from 25 RCTs range from 15.7-40.1 months.

Across all sub-group analyses, OS was not significantly different between AIs and TAM. Only third generation AIs showed a significant advantage in terms of both TTP and CB.

The main weakness of this review is that there is no formal assessment by the authors of the included studies. This means that it is not possible to know whether the studies are good enough to answer to question. Ordinarily such a negative point would downgrade a systematic review but, in this case, four of the studies have been reviewed elsewhere and were found to be of good quality. It therefore seems likely that the authors were rigorous in their selection but did not describe their methodology.

Eisen A *et al.* (2004)

Design: Systematic Review and Guideline (therapy) Evidence level: 1++

Country: Canada (federal state, Commonwealth Realm)

Inclusion criteria:

Included studies:

Selective aromatase inhibitors as first-, second- or third-line hormonal therapy in postmenopausal patients with stage IV breast cancer were evaluated using a randomized controlled design, meta-analysis, evidence-based clinical practice guideline format, or non-comparative design (in the absence of randomized controlled trials).

Clinical trial results were reported in either full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. These data often appear first in meeting abstracts and may not be published for several years.

Exclusion criteria:

Articles excluded from this systematic review included:

Trials of aminoglutethimide (a first-generation aromatase inhibitor) compared to non-aromatase-inhibitor hormonal therapies.

Trials of fulvestrant, formestane, vorozole, or fadrozole (unavailable in Ontario).

Trials of aromatase inhibitors as adjuvant or neo-adjuvant therapy.

Letters and editorials.

Population:

Number of patients = 6652

Interventions:

Selective aromatase inhibitors as first-, second- or third-line hormonal therapy in postmenopausal patients with stage IV breast cancer

Outcomes:

Survival: Quality of life; tumour response (complete response (CR), partial response (PR); Time to progression (TTP); Adverse effects;

Note that clinical benefit includes objective response and stable disease for ≥ 24 weeks, and time to treatment failure (TTF) is the time from randomization to the earliest occurrence of one of three outcomes: progression, death, or withdrawal from randomized treatment.

Follow up:

N/A

Results:

See Cancer Care Ontario guideline:

<http://www.cancercare.on.ca/pdf/pebc1-5f.pdf>

First Line Therapy:

Pooled response rate from 5 randomized trials of aromatase inhibitors versus tamoxifen as first-line therapy for metastatic breast cancer: RR = 1.37 (95%CI: 1.04-1.81) favouring AIs

Pooled 12-month disease-progression rates from 4 randomized trials of aromatase inhibitors versus tamoxifen as first-line therapy for metastatic breast cancer: RR = 0.82 (95%CI: 0.76-0.88) favouring AIs

Because data from abstracts may be less reliable than those from published reports, first the meta-analysis was repeated without the Milla-Santos *et al.* (2001) and Dirix *et al.* (2001) trials. This sensitivity analysis detected pooled RR = 1.23 (95%CI: 0.93-1.61) for response and R = 0.82 (95%CI: 0.77-0.88) for TTP. The pooled result for progression is consistent with that for the full set of four studies, but the overall RR for response becomes non-significant when the analysis is restricted to the three studies reported in full.

Second Line Therapy:

Messori *et al.* (2000) published a meta-analysis of survival data from four of the randomized trials of aromatase inhibitors versus megestrol acetate (see table). This analysis found that treatment with aromatase inhibitors prolonged survival, compared to megestrol acetate, with a RR of death = 0.79 (95%CI: 0.69-0.91) P = 0.0011.

Third Line Therapy:

The findings of 3 phase II studies of the steroidal selective aromatase inhibitor exemestane as third-line (or greater) therapy for metastatic breast cancer (see table) confirm that there is a complete or partial response rate ranging from 7-26% of included trial patients; a range of median TTP of 4.9-14.7 months; and the data suggest that there may be a lack of cross resistance between exemestane and the non-steroidal aromatase inhibitors.

Quality of Life:

Variables related to quality of life were measured with various scales and were taken from one randomised trial of first-line therapy with aromatase inhibitors (Mouridsen *et al.*, 2001) and five randomised trials of second-line therapy (Buzdar *et al.* (2000, 2001), Jonat *et al.* (1996), Dornbrowsky *et al.* (1998), Weinfurt *et al.* (1998) and Kauffmann *et al.* (2000)).

Karnofsky Performance Status (KPS) was measured before and after treatment for all but one participant in the double-blind randomised trial by Mouridsen *et al.* (2001). 15% of women treated with letrozole as first-line therapy experienced an improvement of 20 points or more in KPS score compared with 9% on tamoxifen (P = 0.066). The median time to a worsening of KPS score by 20 points or more was not reached in the letrozole group and was 30 months in the tamoxifen group (log-rank P = 0.002).

The Rotterdam Symptom Checklist and other measures were used to assess quality of life during the first year after randomisation in the Buzdar *et al.* (1997) and Jonat *et al.* (1996) open-label trials of anastrozole versus megestrol acetate as second-line therapy. Buzdar *et al.* reported significantly better physical and psychological scores with anastrozole compared to megestrol (P < 0.025). Jonat *et al.* found the opposite effect, reporting better scores on the psychological dimension of the quality-of-life questionnaire with megestrol (P = 0.008 vs. 1 mg anastrozole, P = 0.003 vs. 10 mg anastrozole) among 75% of trial participants who completed the questionnaire 12 weeks after randomization. Patients on 10 mg anastrozole experienced less bone pain than those on megestrol (P = 0.011), and those on 1 mg anastrozole had better performance status scores at 12 weeks vs megestrol (P = 0.007).

The European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30) scale was used to assess quality of life during the first 24 months of

participation in the double-blind trial of two doses of letrozole versus megestrol acetate by Dombernowsky *et al.* (1998). No significant differences in quality-of-life scores were found among treatment groups but fewer patients on 2.5 mg letrozole experienced a deterioration in World Health Organization (WHO) performance status (41% vs. 55% with megestrol, $P = 0.01$). Buzdar *et al.* (2001) used a similar approach in their double-blind trial of letrozole versus megestrol acetate but found no significant differences among treatment groups in measures of quality of life.

The study by Kaufmann *et al.* (2000) also assessed subjective response and quality of life in their double-blind trial of exemestane versus megestrol acetate. There was no significant difference between treatments in improvement in pain score or tumour-related signs and symptoms. Some of the quality-of-life domains on the EORTC QLQ-C30 were better in the exemestane group ($P < 0.01$ compared with megestrol for physical functioning, role functioning, global health, fatigue, dyspnoea, and constipation) while others improved more in the megestrol acetate group (emotional function, appetite, and pain; p-values not reported).

Toxicity of Selective Aromatase Inhibitors:

In general, therapy with selective aromatase inhibitors is very well tolerated. A full table of adverse events for each study are published with the review. There were no reported deaths that were considered by the investigators to be related to the use of aromatase inhibitors in these trials.

Recommendations from members of the Breast Cancer Disease Site Group Target Population (Cancer Care Ontario Program): *These recommendations apply to post menopausal women with stage IV breast cancer who are candidates for hormonal therapy.*

First-line therapy

- Letrozole and anastrozole are modestly superior to tamoxifen (in terms of objective response rate and time to disease progression) as first-line therapy for postmenopausal women with stage IV breast cancer and are the preferred treatment option in this setting.
- Tamoxifen remains an acceptable alternative.
- There are insufficient data to recommend any one aromatase inhibitor over others in this setting.

Second-line therapy

- Letrozole, anastrozole, and exemestane inhibitors are superior to megestrol acetate or aminoglutethimide as second-line hormonal therapy and are the preferred treatment option in this setting.
- There are insufficient data to recommend any one aromatase inhibitor over others in this setting.

Third- or greater-line therapy

- For postmenopausal women with advanced breast cancer that have been heavily pre-treated with hormonal agents and chemotherapy, exemestane is an acceptable therapy.

Qualifying Statement

- Selective aromatase inhibitors are contraindicated in premenopausal women.

General comments:

This report comprises of a systematic review and the Practice Guideline (developed by the Practice Guideline Initiative's Breast Cancer Disease Site Group). The guideline was appraised using the AGREE tool and found to be of high standard.

The practice guideline report was reviewed and approved by the Breast Cancer Disease Site Group, which includes surgeons, medical oncologists, radiation oncologists, pathologists, a research methodologist, a medical sociologist, a nurse representative, and patient/survivor representative. The report has also been externally reviewed by Ontario practitioners (via a

mailed survey).

Evidence for the systematic review was originally searched up to 2001. It was then updated with a search conducted through to 2003. The databases included in the search were MEDLINE and CANCELIT, the Cochrane Library and databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the San Antonio Breast Cancer Symposium.

To estimate the overall effect of aromatase inhibitors versus tamoxifen as first-line therapy on response and time to disease progression, data were abstracted from the published reports of individual randomized trials and pooled using the Review Manager software. For the pooled analysis of tumour response, the numbers of patients with a complete or partial response were abstracted from the text or tables in published reports, abstracts, or poster presentations. TTP data were obtained by estimating the number of patients who progressed or died within 12 months after randomization from the Kaplan-Meier probability curves presented in each report. These numbers and the numbers randomized were used for the meta-analysis.

12 RCTs, 3 phase II trials and 3 published meta-analyses were eligible for inclusion in this systematic review of the evidence. No relevant evidence-based practice guidelines were found. The update searches found published reports of updates for two publications that had been included in the original evidence summary: the first was an update to a large randomized trial and the second was a meta-analysis of individual-patient data from two trials.

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Updated evidence (4.2)

Summary

Three RCTs (Chia *et al.* 2008, Mouridsen *et al.* 2007 and Goss *et al.* 2007) and a small comparative study (Catania *et al.* 2007) were identified to update the evidence on endocrine therapy for metastatic breast cancer. The total patient number across all trials was 2,522.

Chia *et al.* (2008) presented RCT data from the EFECT study, comparing i.m. fulvestrant with oral exemestane in women whose metastatic breast cancer had progressed on non-steroidal AI therapy. The authors concluded that the drugs had shown equivalent clinical benefit (~32% OR = 1.03 (95%CI: 0.72-1.487)) in a good proportion of women, were both well tolerated with similar adverse events and quality of life reported. Since the route of administration differs in the two treatments it was suggested that patients may make a choice of therapy on this factor.

Mouridsen *et al.* (2007) described a large phase III double blinded, double dummy RCT comparing letrozole (LET) with tamoxifen (PO25 study) as first line therapy for women with advanced and/or metastatic breast cancer. LET significantly improved OS vs TAM over the first 24 months. The advantage was maximal at 14 months and significant for several time points beforehand (every 6 months to 24 months). However, at 36 months the advantage was lost since the survival curves crossed at this point, a phenomenon that could not be explained with certainty. Time to progression was superior in the LET arm (HR = 0.72 (P<0.0001)). The authors concluded that LET had demonstrated overall superiority over tamoxifen as first line therapy and with few reported adverse events.

Goss *et al.* (2007) presented a high quality paper which described a double blinded, double dummy phase III trial comparing atamestane + toremifene with letrozole in the first line treatment of advanced and/or metastatic breast cancer. There were no significant differences between study arms in any measured outcome including time to progression, response, survival or adverse events. The authors concluded that the combined therapy could not be supported in preference to letrozole but suggested that more potent SERMs and selective ER down-regulators might be combined with aromatase inhibitors to provide a more complete oestrogen blockade.

Catania *et al.* (2007) described a small comparative, but non-randomised, study in which women with metastatic breast cancer received fulvestrant, either after disease progression on a previous hormone therapy or as maintenance therapy after chemotherapy. All women had been heavily pre-treated and received only small benefit from this additional therapy (median TTP was 3 months across all participants). The authors felt, however, that fulvestrant could safely be used in such patients in order to lengthen the time before chemotherapy would be required and hence might improve the quality of life for that short period.

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Evidence tables

Question: What is the most effective hormone treatment for metastatic breast cancer?

Created by: Karen Francis on 24/06/2008

Chia <i>et al.</i> (2008)
Design: Randomised controlled trial (therapy) Evidence level: 2- Country: Canada (federal state, Commonwealth Realm)
Inclusion criteria: Post-menopausal women with locally advanced or metastatic breast cancer Relapse on or within 6 months of prior non-steroidal aromatase inhibitor (AI) therapy ER and/or PR positive endocrine status WHO status of 0-2 Life expectancy of at least 3 months At least one measurable or assessable lesion Up to one chemotherapy regimen for advanced breast cancer was admissible Written informed consent
Exclusion criteria: Life threatening metastatic visceral disease Leptomeningeal metastases Prior exposure to fulvestrant or exemestane Extensive RT or cytotoxic therapy within previous month History of bleeding diathesis or requirement for long term anti-coagulation therapy
Population: Number of patients = 693. Age range = 32 to 91 years. Median age = 63 years
Interventions: [1] Fulvestrant arm (n=351): fulvestrant at 250 mg per 5 ml (x2) as an i.m. injection or a matching i.m. 5 ml placebo on day 1 followed by 250 mg in 5 ml or placebo on days 14 and 28 days. Treatment after day 28 was every 28 days (\pm 3 days) thereafter. [2] Exemestane arm (n=342): Oral exemestane at 25 mg, or matching placebo, once a day. Patients continued on treatment until objective disease progression or other events requiring

withdrawal.

Outcomes:

Primary outcome: time to progression (TTP)

Secondary outcomes: objective response ratio (OR), clinical benefit rate (CBR), response duration (RD), overall survival (OS) and tolerability. Quality of life (QOL) was assessed by the FACT-ES instrument

Follow up:

Patients were followed up until their death or, if they withdrew from the trial before disease progression, they were followed up for response until progression and death. Patients were seen by a physician every month for the first 6 months and six-monthly thereafter. Tumour response was assessed every 8 weeks for the first 6 months and then every 3 months until progression.

Median follow-up for all surviving patients was ~13 months.

Results:

At the time of analysis, 288 women in the fulvestrant arm vs 299 in the exemestane arm had experienced disease progression.

Median TTP in both groups = 3.7 months (HR = 0.93, 95%CI: 0.819-1.133) (nsd).

OR: no of women responded to therapy: fulvestrant = 20 vs exemestane = 18. Odds ratio: 1.12 (95%CI: 0.578-2.186) (nsd).

CBR: fulvestrant = 32.2% vs exemestane = 31.5%. Odds ratio: 1.03 (95%CI: 0.72-1.487) (nsd).

Median RD from assignment: Fulvestrant = 13.5 months vs exemestane = 9.8 months

Median RD from 1st response: Fulvestrant = 7.5 months vs exemestane = 5.5 months

Adverse events:

Fulvestrant: 2% of women withdrew because of adverse events vs exemestane (2.6%). Both drugs were well tolerated. The most common adverse events in both arms were hot flushes, injection site pain, nausea and fatigue. QOL assessment showed no significant difference between arms in this respect.

General comments:

This paper describes results from a randomised, double blind, double dummy, phase III trial (EFECT) which compared the efficacy and tolerability of fulvestrant to exemestane in post-menopausal women with endocrine positive breast cancer whose disease has progressed on non-steroidal AI therapy. Participants were recruited between August 2003 and November 2005 from multiple centres.

Baseline characteristics between study arms were generally well balanced but there were more women in the fulvestrant arm with positive endocrine receptor status. ~60% of women had received two or more lines of hormone therapy before study entry.

At the time of data analysis, 34% of participants had died and hence no formal analysis of median overall survival was possible.

The authors conclude that the EFECT trial had demonstrated that both fulvestrant and exemestane had shown clinical activity in a good proportion of women, were both well tolerated with similar adverse events and quality of life reported. Since the route of administration differs in the two treatments it was suggested that patients may make a choice of therapy on this factor.

This multi-centre trial appears to have been thoroughly conducted but this report contains no details of randomisation, allocation or tumour assessment i.e. by whom performed and if blinded

meaning that since bias cannot be eliminated the paper is downgraded in evidential value. A lack of placebo comparator also means that it is not possible to assess the true clinical activity of either treatment arm.

Mouridsen (2007)
Design: Randomised controlled trial (therapy) Evidence level: 2- Country: Denmark
Inclusion criteria: Post menopausal women with breast cancer (defined as stage IIIB ABC) Locoregional recurrent disease not amenable to RT or surgery or metastatic disease Measurable or assessable disease ER and/or PR positive endocrine status (HR unknown was acceptable) One prior chemotherapy regime for metastatic disease acceptable Written informed consent
Exclusion criteria: Recurrence during or within 12 months of prior adjuvant hormone therapy Prior endocrine therapy for advanced breast cancer
Population: Number of patients = 907, age range: 31 to 96 years. Median age: 64/65 years
Interventions: [1] Oral letrozole (LET) at 2.5 mg daily (n=453) [2] Tamoxifen (TAM) at 20 mg daily (n=454) Both drugs were given until disease progression at which point participants were offered the opportunity to cross over to the other arm (blinding was maintained). If endocrine therapy was discontinued participants were treated with trastuzumab, chemotherapy and bisphosphonates as indicated.
Outcomes: Primary outcome: time to progression (TTP) Secondary endpoints: tumour response: overall response rate (ORR), complete response (CR), partial response (PR), time to treatment failure (TTF), clinical benefit rate (CBR), response duration (RD), overall survival (OS) and tolerability.
Follow up: 907 patients were included in an ITT analysis of which 467 crossed over to other study arm (239 to TAM and 228 to LET) due, with the exception of 8 women, to disease progression. 75 patients continued on 1st line therapy without progression and 361 terminated 1st line therapy without crossing over. NB 4 participants in the LET arm were unaccounted for in the analysis.
Results: Efficacy: Median TTP: LET vs TAM arm = 9.4 months vs 6.0 months. HR = 0.72 (P<0.0001) Number of women who experienced PD: LET vs TAM arm = 359 (79%) vs 387 (85%) Multivariate analysis of pre-defined covariates confirmed the advantage of LET vs TAM regardless of receptor status, prior adjuvant TAM therapy or dominant site of metastatic disease (HR = 0.70 95%CI: 0.60-0.81 P<0.0001). The risk of progression was increased by the presence of visceral or bone dominant disease. LET was highly significantly superior to TAM for each individual covariate (all P=0.0001). One prospective analysis also showed that median TTP was longer for LET vs TAM in different age groups. ORR: LET vs TAM arm = 32% vs 21% (P = 0.0002)

CR: LET vs TAM arm = 9% vs 3% (P = 0.0004)
Rate of treatment failure: LET vs TAM arm = 75% vs 85%
Median TTF: LET vs TAM arm 9 months vs 5.7 months (P < 0.0001)
Probability of achieving a complete or partial response: LET vs TAM arm = OR 1.80 (95%CI: 1.32-2.47) P = 0.0002
Multivariate analysis (using the same covariates as above) showed that the probability of treatment failure was increased by prior adjuvant TAM and the presence of visceral or bone metastases.

Survival:

Median OS: LET vs TAM arm = 34 months vs 30 months (P=0.53) (nsd)

LET significantly improved OS vs TAM over the first 24 months and this advantage was maximal at 14 months and significant for several time points beforehand (every 6 months to 24 months). The authors hypothesised that the loss of significance overall may have been influenced by the trial design since the Kaplan Meier survival curves crossed at 36 months, a point at which most women had crossed over to the other study arm or were receiving different 2nd line treatments.

The authors looked at survival in participants after crossover and reported a benefit in median OS (31 months, 95%CI: 22-40) for women crossing to LET compared with women crossing over to TAM (19 months, 95%CI: 17-24). Another analysis, of patients who did not cross over, also highlighted a benefit of LET vs TAM for median OS (35 months (95%CI: 29-43) vs 20 months (95%CI: 16-26).

Safety:

Both LET and TAM were well tolerated and the incidence of reporting adverse events were similar in both (38% vs 37% respectively). The main symptoms were hot flushes (16% vs 13% respectively), nausea (both 6%) and hair thinning (5% vs 3% respectively)

General comments:

This paper describes a large phase III randomised, double blinded, and double dummy trial comparing letrozole with tamoxifen (PO25 study) as first line therapy for women with endocrine receptor positive advanced and/or metastatic breast cancer. The trial was conducted across 201 centres in 29 countries.

The study arms were well balanced with no obvious differences between the two treatments. 93% of the entire population had metastatic disease (~61-63% soft tissue, bone 50-54% and viscera 43-46%).

The overall survival curves for LET and TAM crossed over at 36 months – such a phenomenon violates the assumption of proportional hazards and could indicate a differential effect of an intervention i.e. better than the comparator in the early months but disadvantageous later, or vice versa, but showing no difference overall. By the time of the curves crossed over in this trial, however, the majority of the participants were not taking their originally assigned therapy which confounds the results and makes interpretation difficult, despite several analyses.

The authors concluded that LET demonstrated consistent superiority over tamoxifen for first line therapy. The study appears to be sound but in this report (but perhaps not in others of this trial) there were no details of allocation, randomisation or blinding, other than to say that they had been done. Tumour assessments may not have been conducted by independent investigators and the chances of bias across such a high number of treatment centres is high, all of which downgrades this paper in evidential value.

Goss *et al.* (2007)

<p>Design: Randomised controlled trial (therapy) Evidence level: 2+ Country: USA</p>
<p>Inclusion criteria: Postmenopausal women >18 years of age with locally advanced, recurrent or (locally) metastatic disease not treatable with RT or surgery and/or distant metastases Pathological or histological confirmation of breast cancer ECOG = 0-2 Predicted life expectancy > 12 weeks ER +ve and/or PR +ve Bidimensionally measurable disease Concurrent bisphosphonate treatment was acceptable Written informed consent</p>
<p>Exclusion criteria: Prior endocrine therapy for recurrent, locally advanced or metastatic disease Prior adjuvant AIs or anti-oestrogens or SERMS within 12 months of the study Life threatening disease requiring chemotherapy History of known CNS metastases, significant CNS dysfunction or other active malignancy (other BCC or CIS) Normal (defined) laboratory parameters Previous or planned use of investigational drug within 30 days of enrolment Contradictions to the use of toremifine (TOR), atamestane (ATA) or letrozole (LET)</p>
<p>Population: Number of patients = 865, median age: 63-65 years</p>
<p>Interventions: [1] ATA + TOR arm (n=434): Toremifine (TOR) at 60 mg per day and atamestane (ATA) at 100 mg five times daily. [2] LET arm (n=431): Letrozole (LET) at 2.5 mg given with 5 tablets of placebo given at the same times as in the other arm with respect to time of day, food etc.</p> <p>Patients continued treatment until disease progression or until other reasons, such as toxicity or withdrawal of consent. Post-study treatment was at the discretion of the investigator.</p>
<p>Outcomes: Primary outcome: time to progression (TTP) Secondary outcomes: overall response (OR = CR+PR), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), overall clinical benefit (OCB = OR + SD) time to treatment failure (TTF), survival, adverse events</p>
<p>Follow up: All patients were accounted for. 36 patients in the ATA + TOR arm and 34 patients in the LET arm were not assessable for response</p>
<p>Results: Efficacy: Median TTP: LET vs ATA + TOR = 11.2 months (both) HR = 1.0 (95%CI: 0.91-1.08) (nsd) Median TTF: LET vs ATA + TOR = 9.24 vs 10.44 months HR = 0.99 (95%CI: 0.92-1.06) (nsd) Median OS: LET vs ATA + TOR = 2.79 years vs 3.01 years HR = 0.98 (95%CI: 0.87-1.11) (nsd) OR: LET vs ATA + TOR = 30% (95%CI: 26-35) vs 36% (95%CI: 31-40) OR = 1.27 (95%CI: 0.96-1.69) (nsd) SD: LET vs ATA + TOR = 21% vs 18% PD: LET vs ATA + TOR = 40% vs 39% OCB: LET vs ATA + TOR = 52% (95%CI: 47-56) vs 54% (95%CI: 49-58) OR = 1.08 (95%CI: 0.83-1.41)</p>

<p>Safety: There were no significant differences between treatment arms with respect to adverse events. Those reported in more than 10% of the study population included asthenia, weight gain and hot flushes.</p>
<p>General comments: This high quality paper presents the findings of a randomised, double blind, controlled phase III trial comparing atamestane plus toremifine with letrozole in the first line treatment of advanced and/or metastatic breast cancer. Participants were treated at one of 60 participating centres across 4 countries and were recruited between July 2002 and February 2005.</p> <p>Methods of allocation, randomisation and blinding were very adequately described and were appropriate. Data were analysed from the ITT population. Baseline variables were well balanced between study arms. 70% of participants had soft tissue and/or bone metastases and 80% of patients were treatment naïve (no prior chemotherapy or endocrine therapy). Details of potential conflicts of interest were provided.</p> <p>Given the very similar survival and efficacy results between study arms, the authors concluded that the combined therapy could not be supported in preference to letrozole but suggested that more potent SERMs and selective ER down-regulators might be combined with aromatase inhibitors to provide a more complete oestrogen blockade.</p>
<p>Catania <i>et al.</i> (2007)</p>
<p>Design: Comparative study (therapy), evidence level: 3 Country: Italy</p>
<p>Inclusion criteria: Post-menopausal women with a histologically or cytologically confirmed metastatic breast cancer ER +ve and/or PR +ve tumours as assessed by IHC Previous treatment with at least one prior endocrine therapy for MBC Evidence of disease not amenable to treatment with curative intent At least one measurable lesion WHO status ≤ 2 Life expectancy greater than 3 months Adequate liver, renal and bone marrow function Complete or partial response to previous endocrine therapy for MBC</p>
<p>Exclusion criteria: Life threatening visceral, metastatic disease Active CNS disease Symptomatic pulmonary Lymphangitic disease Previous treatment with fulvestrant Concurrent chemotherapy or chemotherapy within the previous month.</p>
<p>Population: Number of patients = 57, age range: 33 to 85 years. Median age: 63 years</p>
<p>Interventions: [1] Fulvestrant at 250 mg i.m. injection on day 1 and then every 28 ± 3 days thereafter for women after disease progression on a previous hormone therapy (n=27) [2] Fulvestrant as above for women as maintenance therapy after chemotherapy (n=30)</p> <p>All patients were treated until disease progression, unacceptable toxicity or withdrawal of consent.</p>
<p>Outcomes:</p>

Overall response (OR = CR+PR), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), overall clinical benefit (OCB = OR + SD) time to treatment failure (TTF), survival, time to progression (TTP), safety, response duration (RD) and adverse events

Follow up:

Baseline tests included medical history, ECG, blood counts and biochemical assessments, tumour evaluation and performance status. Patients were monitored for clinical and laboratory parameters every 28 days and objective tumour response was measured every 12 weeks. After disease progression, survival was monitored by clinical examination or telephone contact.

All patients were followed up for progression and survival. Mean duration of follow-up was 14 months (range: 11-24). All patients completed the planned treatment and were evaluable for response. At the data cut-off, 22 patients had died.

Results:

Efficacy:

PR = 1 (2%)

OR = 2%

SD = 24 (42%, 95%CI: 29-55) (11 patients had SD for \geq 24 weeks)

PD = 32 (56%, 95%CI: 43-69)

OCB = 21%

Median TTP for the patients (n=30) who had progressed = 3 months (range: 1-15)

Median TTF = 3 months (range: 1-15)

Median OS = 20 months (range: 3-32+)

There were no statistically significant differences in TTP, TTF or survival between patients receiving therapy in groups 1 and 2.

Adverse events:

No patients experienced haematological toxicity. Grade I events included asthenia (n=4), abdominal pain (n=2), hot flushes (n=2), myalgia (n=1), bone pain (n=1) and constipation (n=1).

General comments:

This paper describes a small comparative study of 57 women who had been heavily pre-treated for advanced breast cancer and were given fulvestrant after progressing on previous endocrine therapy or after chemotherapy. This study was part of the 'Faslodex' Compassionate Use Programme and was conducted between December 2003 and May 2005.

Liver and lung metastases were present in 54% and 13% respectively; 67% of patients had bone metastases and 12% had skin involvement. Most patients were heavily pre-treated – the median number of previous lines of endocrine therapy was three (range: 1-7) and all patients had received tamoxifen (sometimes as adjuvant therapy) and aromatase inhibitor for advanced disease.

The activity of fulvestrant differed depending on prior treatment (greater clinical benefit for those having had less than 2 prior therapies regardless of prior response) but not, apparently, according to the two groups in which patients had been placed for this study, albeit on a non-randomised basis. The authors concluded that this drug could safely be used in heavily pre-treated patients in order to lengthen the time before chemotherapy would be required and hence could improve the quality of life for that period.

Health Economic Summary

Evidence Summary

This question yielded a relatively large evidence base so the review criteria were tightened to include those studies that were most relevant to the decision problem; thus only studies taken from the perspective of the UK NHS were reviewed. A total of five studies met the stricter

inclusion criteria from an initial search which identified 358 papers. No additional papers were identified in an update search. None of the economic evaluations compared hormone therapy with a 'do-nothing' alternative, probably due to the fact that hormone therapy in postmenopausal women with advanced breast cancer is standard clinical practice. Neither did any of the evaluations compare all the relevant interventions against each other.

The three older studies evaluate various third-generation aromatase inhibitors (AIs) against Megestol as second-line treatment which was the standard hormone therapy at the time. The more recent studies evaluate Letrozole against Tamoxifen as first-line treatment, in line with current clinical practice.

Study	Line of therapy	Intervention	Comparison
Karnon and Jones, 2003	first	Letrozole	Tamoxifen
Karnon and Johnston et al, 2003	first	Letrozole (then tamoxifen)	Tamoxifen (then letrozole)
Lindgren et al 2002	second	Exemestane	Megestrol
Drummond et al, 1999	second	Anastrozole	Megestrol
Nuijten et al, 1999	second	Letrozole	Megestrol

All studies presented cost-effectiveness analyses (results in terms of cost per life years gained) and the two Karnon papers also presented cost-utility analyses (results in terms of cost per QALYs gained). Since we are investigating the use of AIs in the treatment of patients with advanced breast cancer, a consideration of quality of life is particularly important.

All studies used modelling techniques to model the decision problem over a lifelong time horizon. This meant included the costs and health benefits associated with subsequent treatment. All papers used RCTs to inform the clinical data and costs from nationally published sources. The Karnon and Jones and the Nuijten analysis used a similar model structure that was more comprehensive than the other models, using a Markov process and allowing for various clinical pathways subsequent to hormone treatment. Expert opinion was ascertained using formal methods of elicitation in these studies.

None of the studies used the current discounting recommendation of 3.5% for both health benefits and costs; many of the studies used differential discount rates. By using a lower discount rate for health benefits these studies will have overestimated future health benefits of the interventions which would result in higher incremental cost effectiveness ratios than have been reported. However since the time horizon is not long (lifetime perspective yet never more than 6 years) this effect is not likely to change the conclusions from the studies.

All baseline ICERs for the comparison between Letrozole or Anastrozole and Tamoxifen were below £5,075 per life year gained and £9,200 per QALY. Similar results were obtained for Letrozole, Anastrozole or Exemestane versus Megestrol with a maximum ICER of £9,667 per life year. All of these results were tested to varying degrees of sophistication with sensitivity analysis and were robust to all scenarios presented. However a major limitation of the studies was that all were supported by the pharmaceutical industry. Since not all assumptions were tested, bias from this source cannot be ruled out. In addition none of the studies compared third-generation aromatase inhibitors against each other, so there is no evidence as to which AI is most cost-effective, in either the first- or second- line setting.

An independent analysis would be useful, especially if it incorporated indirect comparison methods to compare all the interventions of interest against each other. This was not undertaken as part of the economic work for this guideline since it was felt that the evidence showed all the baseline ICERs for new AIs in first- or second-line fall within an acceptable level of cost-effectiveness; thus independent modelling on this topic was not considered a high priority.

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Evidence Tables

Question: In patients with metastatic breast cancer, which hormone treatment is most cost-effective?

Created by: Sarah Willis and Christoph Rollig on 11/09/07 (updated by Sarah Willis on 16/07/08)

Full bibliographic reference	Karnon J, Jones T. A stochastic economic evaluation of letrozole versus tamoxifen as a first-line hormonal therapy: For advanced breast cancer in postmenopausal patients. <i>Pharmacoeconomics</i> 2003;21(7):513-525.
Source of funding	Novartis Pharmaceuticals UK (manufacturers of letrozole)
Economic study type	Cost-effectiveness analysis was conducted using a Markov model structure adapted from a model design published by Nuijten and co-workers (1999) (included in this review, see 1.5) which evaluated second-line hormonal therapy.
Population, country & perspective	Postmenopausal women with advanced breast cancer. UK NHS perspective.
Comparison(s)	Letrozole (2.5mg daily) vs. Tamoxifen (20mg daily) as first-line hormonal therapies.
Source of effectiveness data	All effectiveness data are derived from one RCT, Mouridsen et al 2001. Data were used on the probability and timing of serious adverse events (2% with letrozole, 3% with tamoxifen), the proportion of patients progressing, the time to progression, details of subsequent therapy, proportion of patients dying and the time to death.
Cost components	Cost year 2000, GBP. Included: 1 st line therapy cost including: <ul style="list-style-type: none"> - Drug acquisition costs (BNF 40, 2000) - treating serious adverse events (UK NHS HRG costs) - patient consultations (resource use from Nuijten et al 2000, unit costs from NHS reference costs, 2000 and PSSRU costs, 2000) - lab tests (ranging between £2.50 - £68.63; NHS Reference costs, 2000) - other procedures - concomitant drug interventions 2 nd line therapy costs:

	<ul style="list-style-type: none"> - Drug acquisition costs (BNF 40, 2000) - patient consultations - lab tests (ranging between £2.50 - £68.63; NHS Reference costs, 2000) - hospitalisation (Cost per day: General medicine £223, Oncology £334, Palliative care £169; PSSRU costs, 2000) <p>3rd line therapy costs:</p> <ul style="list-style-type: none"> - progesterone megestrol <p>Cost of further treatment/care:</p> <ul style="list-style-type: none"> - three first-line chemotherapy regimens (not specified) - doxorubicin as 2nd line chemotherapy - palliative care for an average of 1.5 months <p>Excluded: none specified</p>
Time horizon, discount rate	A lifetime time horizon was used. Costs were discounted at 6% per year with health benefits discounted at 1.5% per year.
Results – cost	The lifetime cost per patient receiving letrozole as 1 st line hormonal treatment was estimated to be £11,303 compared to £9,631 for a patient receiving tamoxifen as 1 st line hormonal therapy.
Results – effectiveness	Letrozole was associated with 4.182 life years and tamoxifen with 3.468 life years. QALYs were estimated in a sensitivity analysis but the method used to do so was not explained and the results were only shown in terms of incremental cost per QALY.
Results – adverse events	Whilst serious adverse events (SAEs) from first-line therapy were considered, it is not clear that any other adverse events or toxicity associated with subsequent treatments were considered. The impact of the SAEs is only shown in terms the SAE-related cost per patient per event associated with each intervention (letrozole, £1571; tamoxifen, £2476).
Results –incremental cost-effectiveness	An incremental analysis was conducted and resulted in a cost of £2,342 per life year for letrozole compared to tamoxifen. An incremental analysis was also conducted using QALYs as the outcome measure, resulting in the cost per QALY gained with letrozole compared to tamoxifen of between £2,927 and £3,969. The authors suggest this cost per QALY reinforces the cost-effectiveness of letrozole over tamoxifen but the methods for estimating QALYs were not reported so this result should be interpreted with great caution.
Results-uncertainty	The cost effectiveness acceptability curve (CEAC) presented shows that the probability that letrozole is cost-effective (compared to tamoxifen) is 0.5 at a threshold of around £2,500 per life year. The probability rises to 0.9 at around £5,500 per life year.
Authors' conclusions	The authors concluded that the results of their analysis showed that letrozole is a cost-effective alternative first-line therapy compare with tamoxifen, achieving additional life-years at a mean cost of £2,342. The estimated credible intervals showed that even at the 95 th percentile of the cost-effectiveness range, the ICER was just over £10,000.
General comments	As with all the studies in this review, the major limiting factor in the applicability of this study to answer the question posed for this guideline was that not all the interventions of interest (i.e. all relevant hormone therapies) were evaluated. Although there is no direct clinical evidence comparing all these options, no attempt was made to formally combine indirect evidence. The applicability of this study for the advanced breast cancer guideline is also limited by the fact that the primary outcome measure for the analysis was life years gained. Since quality of life is an important in the consideration of the effect of treatment in patients with advanced breast cancer, the use of QALYs may have been more appropriate. Although this was attempted in a sensitivity analysis the method used to attribute published utility values to different health states was not well described. It should also be noted that this study was funded by the manufacturer of letrozole, Novartis.
Full bibliographic reference	Karnon J, Johnston SR, Jones T, Glendenning A. A trial-based cost-effectiveness analysis of letrozole followed by tamoxifen versus tamoxifen followed by letrozole for postmenopausal advanced breast cancer. <i>Ann Oncol</i> 2003; 14(11): 1629-33.
Source of funding	Novartis (manufacturer of letrozole)
Economic study type	Both cost-utility and cost-effectiveness analysis.

Population, country & perspective	Postmenopausal women with advanced breast cancer. UK NHS perspective
Comparison(s)	First-line letrozole with the option of second-line tamoxifen compared to first-line tamoxifen with the option of second-line letrozole.
Source of effectiveness data	The one phase III RCT (Mourisden et al, 2001) which included a crossover design at the point of disease progression (52% of patients treated with letrozole first switched over to tamoxifen, while 50% patients treated initially with tamoxifen switched over to letrozole).
Cost components	<p>Cost year not stated. All costs given in GBP.</p> <p>Costs included:</p> <ul style="list-style-type: none"> - drugs (BNF, 2002) - patient consultations (PSSRU costs, 2000) - lab tests (PSSRU costs, 2000) - hospitalisation (PSSRU costs, 2000) <p>The resource use for these items was taken from the 1999 Nuijten analysis (also in this review)</p> <p>Costs excluded:</p> <p>None stated</p> <p>All other costs are assumed to be the same for both strategies.</p>
Time horizon, discount rate	Lifetime time horizon. 6% discount rate for costs, 1.5% discount rate for benefits. A discount rate of 6% for both costs and benefits is explored in the sensitivity analysis.
Results – costs	The costs associated with 1 st line letrozole, 2 nd line tamoxifen were estimated as £4,765,088 per 1000 patients (£4,765 per patient). First-line tamoxifen followed by 2 nd -line letrozole was estimated at £3,417,939 per 1000 patients (or £3,418 per patient).
Results – effectiveness	The strategy of starting with letrozole was associated with 1684 life years per 1000 patients (1.684 life years per patient) whilst the strategy of starting with tamoxifen was associated with 1457 years per 1000 patients (1.457 years per patient). The incremental life years with letrozole first (compared to tamoxifen first) is 0.228.
Results – adverse events	No adverse events were considered in the model.
Results –incremental cost-effectiveness	The incremental analysis showed letrozole then tamoxifen was associated with a cost per QALY of £8,514. The cost-effectiveness analysis yielded an ICER of £5,914 per life year gained with letrozole then tamoxifen rather than vice versa.
Results-uncertainty	A series of one- and multi-way deterministic sensitivity analyses were undertaken although there was no justification of the parameters investigated (they increased and decreased the costs by an arbitrary 50%, adjusted the utility values and considered a different discount rate). Probabilistic sensitivity analysis is also reported but it is not clear what distributions were applied to which parameters. The ICER ranged from £4,227 - £16,373 per life year gained and from £6,083 - £23,558 per QALY.
Authors' conclusions	The authors conclude that starting hormone therapy with letrozole is a cost-effective alternative to tamoxifen for the UK NHS. Whilst they admit the 97.5 th percentile yields an ICER of £23,558 per QALY, this is below the implicit threshold of £30,000 per QALY. Other sensitivity analysis on the cost and utility weights show that the results are not sensitive to these values, nor to variations in the discount rate.
General comments	As with all the studies in this review, the major limiting factor in the applicability of this study to answer the question posed for this guideline was that not all the interventions of interest (i.e. all relevant hormone therapies) were evaluated. Although there is no direct clinical evidence comparing all these options, no attempt was made to formally combine indirect evidence. .Again, it should be noted that this study was funded by the manufacturer of letrozole.
Full bibliographic reference	Lindgren P, Jonsson B, Redaelli A, Radice D. Cost-effectiveness analysis of exemestane compared with Megestrol in advanced breast cancer - A model for Europe and Australia. <i>Pharmacoeconomics</i> 2002;20(2):101-108.
Source of funding	Pharmacia Corporation (manufacturer of exemestane)

Economic study type	Cost-effectiveness analysis. Decision analytic model using a markov process.
Population, country & perspective	Postmenopausal women with advanced breast cancer, non-responsive to tamoxifen therapy. Perspective taken was that of a third-party payer in Australia and different European settings, including that of the UK.
Comparison(s)	Exemestane (25mg/day) vs. Megestrol (40mg four times daily)
Source of effectiveness data	One RCT, Kaufmann et al 2000.
Cost components	Price year 1999, EUR. Exchange rate not reported. Costs included: <ul style="list-style-type: none"> - drug costs: cost per day of exemestane €5.60, megestrol €2.13 (retail price, source not stated) - all other treatments, such as in- and out- patient visits, procedures such as surgery and radiotherapy, diagnostic tests, concomitant medication, palliation. (derived from a retrospective observational study) Excluded: none specified
Time horizon, discount rate	Two time horizons used: 36 months and lifetime. Both costs and benefits at 3% p.a.
Results – cost	Total cost with exemestane per patient ranged from €6,556 in Belgium to €16,366 in the UK in the 3 year analysis, and ranged between €9,069 in Belgium to €23,293 in the UK in the lifetime analysis. Three year costs with megestrol per patient ranged from €5,378 to €14,359 in the UK, whereas lifetime costs ranged from €7,066 in Spain to €19,047 in the UK. The high prices in the UK were attributable to the 'Other healthcare' costs rather than the second-line hormonal therapy drug costs. UK: 3yr time horizon: Total cost with exemestane €16,366; with megestrol €14,359 Lifetime horizon: Total cost with exemestane €23,293; with megestrol €19,047
Results – effectiveness	The effectiveness results were assumed to be equally applicable for all countries considered. 3-year time horizon: Exemestane was estimated to be associated with 758.5 days survival compared to 696.3 days with Megestrol. Lifetime horizon: the survival associated was not reported for either alternative.
Results – adverse events	Adverse events were not included in the model, despite being more common in the megestrol arm.
Results –incremental cost-effectiveness	The ICERs ranged from €6,911 in Belgium to €13,016 in the Netherlands. Despite costs in the UK being the highest of all countries, the difference in cost between the two alternatives was greatest in the Netherlands. Since effectiveness was constant across countries the difference in cost was the sole driver of the incremental cost-effectiveness ratios. UK: 3 year horizon: Exemestane was associated with an incremental cost-effectiveness ratio of €11,733 per life year gained compared to megestrol.
Results-uncertainty	Limited one-way sensitivity analysis. The discount rate was varied using a 6% pa rate for costs and 1.5% pa for health benefits and resulted in an ICER of €11,073 per LYG in the 3year analysis.
Authors' conclusions	The authors conclude that exemestane is a cost-effective alternative to megestrol as second-line therapy in the UK. They explain that differences in cost-effectiveness between countries are solely attributable to differences in costs. The authors admit there was no inclusion of adverse events; they would increase the costs of megestrol. Exemestane is a cost-effective option for postmenopausal women with progressive advanced breast cancer after therapy with tamoxifen.
General comments	In addition to the fact quality of life was not explicitly considered in the analysis, and the comparators were limited (which was true of most studies in this review) there were a few other limitations. The sensitivity analysis performed was limited and there was a number of transparency issue in the reporting, for example unit costs were not separated from resource use. The use of two time horizons was interesting as it demonstrated the importance of considering lifetime costs and benefits when evaluating competing alternatives.

Full bibliographic reference	Drummond M, Thompson E, Howell A, Jonat W, Buzdar A, Brown J. Cost-effectiveness implications of increased survival with anastrozole in the treatment of advanced breast cancer. <i>Journal of Drug Assessment</i> 1999;2(2):169-179.																								
Source of funding	Zeneca Pharmaceuticals (manufacturer of anastrozole)																								
Economic study type	Cost-effectiveness analysis.																								
Population, country & perspective	Patient population considered in the analysis was that of the two RCTs: postmenopausal women with advanced breast cancer failing treatment with tamoxifen. Primary analysis – UK. Secondary analyses in the US, Germany and Australia. Perspective taken was of the third-party payer.																								
Comparison(s)	Anastrozole (1mg daily) vs. Megestrol (40mg, four times daily)																								
Source of effectiveness data	Two randomised controlled trials (Buzdar 1996 and Buzdar 1998). It is not clear how data from the two trials were synthesised.																								
Cost components	Only drug acquisition costs were included. Supportive care was assumed to be the same, irrespective of the intervention. A daily cost of £2.97 for anastrozole and £0.97 for megestrol was used (source not reported). Lifetime costs were estimated from the literature, £7,620 over 27 months, (Richards et al, 1993), although it is not clear if these were included in the basecase or just as a sensitivity analysis.																								
Time horizon, discount rate	Neither costs nor benefits were discounted to present values. This was justified by the short time horizon, although it is not clear how long patients are assumed to live. The lifetime costs are for 27 months, but this may be in addition to the 274-371 days spent on megestrol or anastrozole respectively. This may mean that patients are estimated to live well beyond two years in which case discounting would have been appropriate. However since the survival time is undoubtedly short, not applying a discount rate is unlikely to affect the conclusions of the analysis. The time horizon was not explicitly stated, but was assumed to be lifetime.																								
Results – cost per patient per alternative	Not reported.																								
Results – effectiveness per patient per alternative	Median time to death: 26.7 months with anastrozole and 22.5 with megestrol. The 2-year survival rate was 56.1% with anastrozole and 46.3% with megestrol. However mean estimates are used for economic evaluation, and in the basecase analysis these were estimated using an area under the curve analysis. The mean duration of treatment was estimated to be 371 days and 274 days on anastrozole and megestrol respectively. This was associated with 1077 days survival on anastrozole and 887 days survival on megestrol.																								
Results – adverse events	Adverse events were not discussed in the paper, so it is assumed they were not considered in the analysis.																								
Results –incremental cost-effectiveness	The baseline ICER associated with anastrozole compared to megestrol was estimated to be £1,608 per additional life year in the UK. It ranged from just £5 per LYG in Germany, to £1,643 per LYG in Australia.																								
Results-uncertainty	<p>A limited sensitivity analysis was undertaken, investigating the impact of using two different methods to estimate mean survival from the trial data, on the results of the analysis.</p> <p>Estimation of treatment duration and survival by other methods:</p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">Duration of treatment (days)</th> <th colspan="2">Survival (days)</th> </tr> <tr> <th>Anastrozole</th> <th>Megestrol</th> <th>Anastrozole</th> <th>Megestrol</th> </tr> </thead> <tbody> <tr> <td>AUC (basecase)</td> <td>371</td> <td>274</td> <td>1077</td> <td>887</td> </tr> <tr> <td>Weibull</td> <td>369</td> <td>279</td> <td>832</td> <td>661</td> </tr> <tr> <td>Kaplan Meier</td> <td>174</td> <td>145</td> <td>814</td> <td>684</td> </tr> </tbody> </table> <p>The resulting ICERs (in the UK analysis) from the Weibull analysis £1,761 per LYG with anastrozole compared to the Kaplan Meier estimate which yielded £1,056 per LYG with anastrozole.</p> <p>Differences in follow up time observed were investigated, although the range of values was not reported which makes interpreting the results problematic. The ICER was reported to be £3,730 per LYG with anastrozole.</p>		Duration of treatment (days)		Survival (days)		Anastrozole	Megestrol	Anastrozole	Megestrol	AUC (basecase)	371	274	1077	887	Weibull	369	279	832	661	Kaplan Meier	174	145	814	684
	Duration of treatment (days)		Survival (days)																						
	Anastrozole	Megestrol	Anastrozole	Megestrol																					
AUC (basecase)	371	274	1077	887																					
Weibull	369	279	832	661																					
Kaplan Meier	174	145	814	684																					

Authors' conclusions	The authors conclude that the ICER (£1,608 per LYG) associated with anastrozole compared to standard second-line treatment; megestrol falls within an acceptable level of cost-effectiveness and is robust to the sensitivity analysis conducted. They present this conclusion with appropriate caveats, questioning the validity of retrospective data used and how the methods of survival estimation slightly alter the results, though not the conclusions of the analysis. They compare the cost-effectiveness of anastrozole across different countries, which all show anastrozole to be a cost-effective alternative to megestrol, using acceptable willingness to pay thresholds in Canada and the results of recent studies investigating the cost-effectiveness of breast screening programs in the UK. The authors acknowledge the limitations of their analysis; not explicitly considering the impact of the interventions of patients' quality of life, nor taking their preferences into account, nor factoring in possible adverse events, although they suggest these factors would not alter the conclusions of the analysis since the cost per life year gained is very low and utility values would have to be very low to result in an unfavourable cost per QALY.
General comments	This was a simple analysis and some important aspects of the evaluation were not reported, for the costs in particular. In addition only two interventions were compared and quality of life was not considered. However, the resulting ICER was low and does not differ from the other study in the review suggesting that anastrozole is a cost-effective alternative to megestrol as second-line hormone therapy for postmenopausal women with advanced breast cancer.
Full bibliographic reference	Nuijten M, Meester L, Waibel F, Wait S. Cost effectiveness of letrozole in the treatment of advanced breast cancer in postmenopausal women in the UK. <i>Pharmacoeconomics</i> 1999; 16(4):379-397.
Source of funding	Novartis (manufacturer of letrozole)
Economic study type	Cost-effectiveness analysis.
Population, country & perspective	A hypothetical cohort of patients: postmenopausal women with advanced breast cancer who had previously failed to respond to first-line or adjuvant antiestrogen. UK, NHS.
Comparison(s)	2.5mg/day Letrozole vs. 160mg/day Megestrol as second-line hormonal therapy.
Source of effectiveness data	Second-line hormonal therapy: - One RCT, the AR/BC2 trial (Dombernowsky, 1998). Full details were provided about the trial including the inclusion and exclusion criteria, design and results. In addition assumptions were made using expert opinion. Third-line hormonal therapy: - a multi-centre randomised trial (Garcia-Giralt et al, 1992) - a small 1-centre trial (Brufman et al, 1994) - a retrospective study of 55 patients at the Royal Marsden hospital (Iveson et al, 1993) First-line chemotherapy: - 4 randomised studies (3 of CMF) (Alonso et al, 1995; Fraser et al, 1993; Viladiu et al, 1985) - a non-blind randomised study (Hoogstraten et al, 1984) - 2 retrospective analyses (Gerritsen et al, 1995; Gregory et al, 1993) - a review of 9 randomised studies with multi-drug chemotherapy regimens (Mouridsen et al, 1992) Second-line chemotherapy: - a non-blind prospective study (Gregory et al, 1993) - a retrospective analysis (Alonso et al, 1995) - a review of 85 clinical studies (Petru et al, 1986) Observational care and palliative care: - used expert opinion to estimate the probability of disease progression and mortality since no published data exist.
Cost components	Costs were reported as 1996 prices, in GBP. Unit costs and resource use reported separately. Costs derived from Birmingham City hospital (assumed NHS charges were a proxy for real costs). Health care utilisation was estimated by expert opinion using formal elicitation methods. Costs included: (Direct medical costs) - drug therapy (letrozole, megestrol, other hormone therapies, chemotherapy, other medication for serious adverse events or pain)

	<ul style="list-style-type: none"> - consultations (GP, oncologist, nursing time) - number of days of hospitalisation (per diem rate, including all procedures and drugs) <p>Market price per unit, 1997 used for:</p> <ul style="list-style-type: none"> - letrozole £2.97 - megestrol £1.01 <p>Excluded: none specified</p>
Time horizon, discount rate	<p>Lifetime time horizon (6.25 years).</p> <p>5% annual discount rate for costs. Not clear if a discount rate was applied to health benefits (none stated). No discussion of why this might have been appropriate.</p>
Results – cost per patient per alternative	Average cost per patient: with letrozole £7,547, with megestrol £6,820.
Results – effectiveness per patient per alternative	Average survival with letrozole was estimated to be 25.2 months, whilst patients treated with megestrol were estimated to live on average 22.8 months, thus a 2.4 months survival attributable to letrozole as second line hormonal therapy.
Results – adverse events	Serious adverse events resulting from second line hormone treatment were considered, but the adverse events arising from further hormonal therapy or subsequent chemotherapy were not considered. Neither was potential toxicity resulting from chemotherapy.
Results –incremental cost-effectiveness	The baseline estimate of cost-effectiveness for letrozole compared to megestrol as second line hormonal therapy was £3,588 per life year gained.
Results-uncertainty	A series of one-way deterministic sensitivity analyses were performed on the main probabilities and cost assumptions used in the analysis. The model was insensitive to changes in costs of hospitalisation, chemotherapy and serious adverse events as these did not impact on the results. An increase in the price of letrozole and the resource use assumptions had some impact on the baseline ICER causing it to increase by £1,863 in the former case and vary between £3239 and £4137 in the latter. The model was highly sensitive to the acquisition costs of letrozole (a 20% increase led to an increase in the ICER to £5,451 per LYG) and megestrol (ICER not reported) and to the efficacy and safety parameters with second-line hormone therapy (ICERs ranged from letrozole dominating the megestrol alternative to £27,702 per LYG when the probability of progression after 3 months on megestrol was increased 0.6).
Authors' conclusions	The authors concluded that Letrozole offers a cost-effective alternative to megestrol as a second-line hormonal therapy from a UK NHS perspective with an incremental cost-effectiveness ratio of £3,588 per life year gained, according to the model presented and given the assumptions that were made. The authors compare the modelled survival outcomes with updated results of the main clinical trial used in the analysis, and although they do differ, the difference between the two alternatives is the same (at around 10%).
General comments	This was a well conducted and thoroughly reported analysis. As with the other studies there was no consideration of quality of life which we know to be particularly important at this stage of the disease. Another limit on the applicability of the results of this study to the review question was that only two alternative therapies were compared.

Drummond Checklist

Question	Karnon & Jones et al. (2003)	Karnon & Johnston et al. (2003)	Lindgren et al. (2002)	Drummond et al. (1999)	Nuijten et al. (1999)
1. The research question is stated.	Yes	Yes	Yes	Yes	Yes
2. The economic importance of the research question is stated.	Yes	Yes	Yes	Yes	Yes
3. The view point(s) of the analysis are stated and justified.	Yes	Yes	Yes	Not fully	Yes
4. The rationale for choosing the alternative programmes or interventions are stated.	Yes	No	No	Yes	Yes
5. The alternatives being compared are clearly described.	Yes	Yes	Yes	Yes	Yes
6. The form of economic evaluation is stated.	Yes	No	Yes	Yes	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	No	No	Yes	No	No
8. The source(s) of effectiveness estimates are stated.	Yes	Yes	Yes	Yes	Yes
9. Details of the design and results of effectiveness study are given (if based on a single study).	Yes	Yes	Not fully	Not applicable	Yes
10. Details of methods of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).	Not applicable	Not applicable	Not applicable	No	Yes
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	Yes	Yes	Yes
12. Methods to value health states and other benefits are stated.	Not clear	Not applicable	Not applicable	Not applicable	Not applicable
13. Details from the subjects from whom valuations are obtained are given.	No	Not applicable	Not applicable	Not applicable	Not applicable
14. Productivity changes (if included) are reported separately.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
15. The relevance of productivity changes to the study question is discussed.	No	No	Yes	No	Yes
16. Quantities of resources are reported separately from their unit costs.	No	Yes	No	No	Yes
17. Methods for the estimation of quantities and unit costs are described.	Yes	Yes	Yes	Not fully	Yes

Question	Karnon & Jones et al. (2003)	Karnon & Johnston et al. (2003)	Lindgren et al. (2002)	Drummond et al. (1999)	Nuijten et al. (1999)
18. Currency and price data are recorded.	Yes	No	Yes	Yes	Yes
19. Details of currency of price adjustments for inflation or currency conversion are given.	Not applicable	Not applicable	No	Yes	Not applicable
20. Details of any model used are given.	Yes	Yes	Yes	No	Yes
21. The choice of model used and key parameters on which it is based are justified.	Not fully	Yes	Yes	Not applicable	Yes
22. The horizon of costs and benefits is stated.	Yes	Yes	Yes	No	Yes
23. The discount rate is stated.	Yes	Yes	Yes	Yes	Not fully (for costs but not explicitly for health benefits)
24. The choice of rate is justified.	Yes	No	Yes	Not applicable	No
25. An explanation is given if costs or benefits are not discounted.	Not applicable	Not applicable	Not applicable	Yes	No
26. Details of statistical test and confidence intervals are given for stochastic data.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
27. The approach to sensitivity analysis is given.	Yes	Yes	Yes	Not fully	Yes
28. The choice of variables for sensitivity analysis is justified.	Not fully	Not fully	No	Yes	Yes
29. The ranges over which the variables are varied is stated.	Not clear	Yes	Yes	Not fully	Yes
30. Relevant alternatives are compared.	Yes	Yes	Yes	Yes	Yes
31. Incremental analysis is reported.	Yes	Yes	Yes	Yes	Yes
32. Major outcomes are reported in a disaggregated as well as aggregated form.	Yes	Yes	Yes	No	Yes
33. The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes
34. Conclusions followed from the data reported.	Yes	Yes	Yes	Yes	Yes
35. Conclusions are accompanied by the appropriate caveats.	No	No	Yes	Yes	Yes
36. Generalisability issues are addressed.	No	No	Yes	Yes	Yes

4.2.2 Men with metastatic breast cancer

Short summary

Three papers (Kantarjian *et al.* 1983, Patel *et al.* 1984 and Lopez *et al.* 1985a) presented case series of men who had received a great variety of endocrine therapies, including surgery. None of the treatments were highlighted for specific analysis and the numbers of each patient sub-group are too low to make a summary of any value.

Otherwise, there were eight retrospective case series (El Omari-Alaoui 2002, Giordano 2002, Harris *et al.* 1986, Lopez 1985b & 1993, Patterson *et al.* 1980 and Ribeiro 1976 & 1983) which reviewed data from case files of male patients treated for breast cancer. The papers spanned nearly three decades and involved 321 males - four papers were from the United Kingdom. None of the studies were comparative and, although of low quality, represent probably the best available evidence on this topic.

Very limited evidence (n=5) suggested that aminoglutethimide may be suitable therapy for men with advanced breast cancer who have been previously orchidectomised. Diethylstilboestrol therapy was effective for men with soft tissue disease but failed to elicit a significant tumour response in those with more widespread metastatic breast cancer.

Limited evidence suggests that cyproterone was an effective therapy in some men but there were no factors by which response could be predicted and the treatment resulted in impotence and loss of libido for many patients. Androgen blockade with buserelin did not appear to enhance the response but may have prevented response flare. A very limited case series (n=5) showed that anastrozole therapy did not result in a positive response in ER +ve males with metastatic breast cancer.

Two poor quality studies reviewed data on treatment with tamoxifen. Some patients were included in both studies. The authors reported objective response rates from 37.5% to 48% and response duration from 1 month to 5 years. Where endocrine status was known, only the ER +ve sub-group was associated with favourable tumour response. Few adverse events were reported.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men with metastatic breast cancer	<ul style="list-style-type: none"> • Aromatase inhibitors • Tamoxifen • GnRH agonists • Stilboestrol • Anti-androgens • Orchidectomy 	Each with each other	<ul style="list-style-type: none"> • Time to progression • Overall survival • Toxicity • QOL • Response rate

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Evidence summary

There were eleven retrospective case series (El Omari-Alaoui 2002, Giordano 2002, Harris *et al.* 1986, Kantarjian *et al.* 1983, Lopez 1985a, 1985b & 1993, Patel *et al.* 1984, Patterson *et al.* 1980 and Ribeiro 1976 & 1983) which reviewed data from case files of male patients treated for breast cancer. The papers spanned nearly three decades and involved 292 males - four papers were from the United Kingdom. None of the studies were comparative and, although of low quality, represent probably the best available evidence on this topic.

In 1976, Ribeiro presented data from 58 men with advanced breast cancer who were given first line oral diethylstilboestrol at three different doses at a single UK centre between 1942 and 1972. An objective response rate of 38% was seen in men who had predominantly soft tissue disease. The response duration for complete responders was 7 years with a median survival of 6 years and 10 months. Non-responders were men with widespread metastatic disease who had a median OS of just over one year.

Ribiero (1983) and Patterson *et al.* (1980) retrospectively reviewed data from men with breast cancer who had been given 20 mg to 40 mg tamoxifen per day for unknown durations. Nine of the men were included in both studies. The authors reported objective response rates of 37.5% and 48% respectively with response duration in a very wide range, between one month and five years. Survival outcomes were not reported in either paper. Few tumours were assessed for endocrine status but in those men in which this had been undertaken, only ER +ve status was associated with tumour response. Few adverse events were reported.

Harris *et al.* (1986) presented five case reports on men with advanced breast cancer who were given aminoglutethimide. One man, the only subject who had been orchidectomised, responded positively to the treatment for 14 months. The other four men failed to respond and yet, although their oestrogen levels were not reduced by this aromatase inhibitor, they all subsequently responded to tamoxifen.

Lopez *et al.* (1985b) reported on a small series of men (n=10) with recurrent or progressive breast cancer who were given cyproterone twice a day for an unknown duration. The objective response rate was 70% and the median duration for responders was 8 months. The anti-androgenic activity of the drug resulted in impotence and there were also reports of gynaecomastia, weight gain and tiredness. The response to treatment was not predicted by any identifiable factor, including hormone levels since response did not always correlate with measured testosterone, oestradiol or gonadotropins. Lopez *et al.* (1993) presented further case reviews in which men (n=11) had received cyproterone with a GnRH analogue, buserelin until disease progression. The objective response rate was 63.6% with median response duration for responders of 11.5 months. Even in those men with stable disease, pain and symptoms were alleviated. Median overall survival was 18.5 months. Both drugs were well tolerated but, again, impotence and loss of libido were commonly reported. The tumour responses were independent of measured hormone levels and the relationship between therapy and endocrine status was not explored (although five men with a positive response were ER +ve/ PR -ve).

Giordano *et al.* (2002) reported on five men who had received anastrozole for the treatment of metastatic breast cancer. Each case was discussed in narrative synthesis. None of the men experienced an objective response although 3/5 had a temporary stabilisation of disease and two men derived a clinical benefit (stable disease > 24 weeks). All men were ER +ve.

Three groups (Kantarjian *et al.* 1983, Patel *et al.* 1984 and Lopez *et al.* 1985a) presented data from men who had received various therapies for advanced breast cancer including orchidectomy, adrenalectomy, hypophysectomy, aminoglutethimide, androgens, oestrogens, corticosteroids, medroxyprogesterone, tamoxifen and stilboestrol. Individual therapies were not discussed but rather endocrine therapy as a whole was assessed for its effect on survival. In

most cases the number of patients receiving any one treatment is so low that summarizing the outcomes is not meaningful.

References

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Evidence tables

Question: What is the most effective hormone treatment for men with metastatic breast cancer?
Created by: Karen Francis on 27/06/2007

Ribiero (1983)
Design: Retrospective case series (therapy), evidence level: 3 Country: UK
Inclusion criteria: Men with inoperable primary breast cancer, recurrent and/or metastatic disease.
Exclusion criteria: None stated
Population: Number of patients = 24, age range: 36 to 86 years. Mean age: 63 years
Interventions: 20/24 men received tamoxifen citrate at 20 mg per day.

<p>4/24 men received tamoxifen citrate according to a schedule: day 1: 160 mg and then 20 mg per day thereafter.</p> <p>No patient received chemotherapy and areas exposed to radiotherapy were excluded from assessment.</p> <p>Therapy was given for a minimum of 2 months to all patients and one patient continued for 5 years.</p>
<p>Outcomes: Tumour response (complete response CR, partial response PR, stable disease SD, progressive disease PD), response duration (RD)</p>
<p>Follow up: Minimum follow-up = 8 months. Maximum follow-up = 60 months.</p>
<p>Results: Efficacy (n=24): CR = 5/24 PR = 4/24 therefore total response = 9/24 (37.5%) SD = 2/24 (each for 24 months) PD = 12/24 Mean RD = 21 months (range: 8-60)</p>
<p>General comments: This paper reports the findings on the treatment of 24 male breast cancer patients given tamoxifen at a single UK centre. Nine of the men were included in another retrospective study (Patterson <i>et al.</i>, 1980). All men had progressive disease, 12 with soft tissue loco-regional disease, 6 also had bone metastases, 3 had bone only disease and 3 had lung only disease.</p> <p>Ten tumour samples were assayed for endocrine receptor status of which seven were ER +ve and 5 were PR +ve. Two of the men with ER +ve cancer failed to respond to tamoxifen although one later responded to bilateral adrenalectomy and orchidectomy. None of the men with ER –ve cancer responded to tamoxifen.</p> <p>No patients reported adverse events from tamoxifen.</p> <p>This paper is a simple reporting of data from patient case notes with no details of assessment methods and is of less evidential value than a comparative study.</p>

Ribiero (1976)
<p>Design: Retrospective case series (therapy), evidence level: 3 Country: UK</p>
<p>Inclusion criteria: Men with recurrent and/or metastatic breast cancer. No previous endocrine therapy</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 58, age range: 33 to 88 years. Mean age: 69 years</p>
<p>Interventions: 54/58 men received oral diethylstilboestrol at 15 mg per day (3 x 5 mg doses)</p>

<p>2/58 men received oral diethylstilboestrol at 20 mg per day.</p> <p>3/58 men received oral diethylstilboestrol at 3 mg per day.</p> <p>Therapy was given for a minimum of 2 months to the majority of patients.</p>
<p>Outcomes: Tumour response (complete response CR, partial response PR), response duration (RD), survival.</p>
<p>Follow up: 2 men withdrew from the study within the first week due to nausea. One patient was lost to follow-up.</p>
<p>Results: Efficacy (n=55): CR = 14/55 PR = 7/55 therefore total response = 21/55 (38%)</p> <p>Median RD for those with CR = 7 years Median RD for those with PR = 1 year</p> <p>Median survival for CR (excluding 3 patients who died of other causes) = 6 years 10 months Median survival for PR = 1 year 7 months Median survival for non-responders (34/55) = 1 year 1 month.</p>
<p>General comments: This paper reports the findings on the treatment of 58 male breast cancer patients given diethylstilboestrol at a single UK centre between January 1942 and January 1972. 27 men had developed post-surgical recurrence, 17 had disease progression after radiotherapy and 14 men presented with widespread disease.</p> <p>All the men who responded to therapy were those with recurrent or progressive soft tissue disease (breast, chest wall and/or lymph nodes) who had been given surgery and/or radiotherapy. 14 men who had widespread disease failed to respond to diethylstilboestrol. 6 men with bone only disease also failed to respond. 2 men had bone and lung disease and whilst the lung metastases responded for five months, overall, the cancer progressed.</p> <p>Very few treatment side effects were reported. Two patients withdrew because of nausea and two patients reported severe gynaecomastia which was not treated with radiotherapy.</p> <p>This paper is a simple reporting of data from patient case notes with no details of assessment methods and is of less evidential value than a comparative study.</p>

<p>Patterson <i>et al.</i> (1980)</p>
<p>Design: Retrospective case series (therapy), evidence level: 3 Country: UK</p>
<p>Inclusion criteria: Men with advanced breast cancer Objectively assessable disease</p>
<p>Exclusion criteria: None stated</p>
<p>Population:</p>

Number of patients = 31, age range: 45 to 88 years. Mean age: 66 years
<p>Interventions: Tamoxifen was given to all patients at doses ranging from 20 to 40 mg per day. The duration of treatment was not given.</p>
<p>Outcomes: Tumour response (complete response CR, partial response PR, stable disease SD, disease progression PD), response duration (RD)</p>
<p>Follow up: One patient died after 1 day of therapy and was excluded from the analysis. One patient received additional corticosteroid therapy.</p>
<p>Results: Efficacy (n=31): CR = 8/31 PR = 7/31 therefore total response = 15/31 (48%) Mean RD = 9+ months (range: 1+ to 30 months)</p> <p>SD = 5/31 (mean duration = 10+ months) PD = 11/31</p>
<p>General comments: This paper presents data extracted from several other publications in which the treatment of a very small number of patients were described (total n=11) plus 21 unpublished patient histories, including 9 that were the subjects of Ribiero's paper (1983) (see above).</p> <p>5/10 of the patients with visceral disease, 2/5 of the men with bone dominant disease and 8/15 with soft tissue disease achieved a positive response.</p> <p>Of the few tumours that were classified for endocrine status, 4/5 patients with ER +ve tumours, but none of 3 men with ER -ve tumours, responded positively to tamoxifen. Few side effects were reported. One man was removed from study with GI intolerance and bone pain; two others had a dose reduction with the advent of mild leukopenia and one man developed hypercalcaemia which resolved after withdrawal of tamoxifen and did not recur after reintroduction.</p> <p>Whilst a review of previous studies was warranted, the author presented a potentially unsafe pooling of data since, for example, investigators may have used different methods of assessing tumour response.</p>

Kantarjian <i>et al.</i> (1983)
<p>Design: Retrospective case series (therapy), evidence level: 3 Country: USA</p>
<p>Inclusion criteria: Men with breast cancer (all stages).</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 41, age range: 30 to 78 years. Mean age: 60 years</p>
<p>Interventions: Various including orchidectomy, androgens, oestrogens, anti-oestrogens and corticosteroids.</p>
<p>Outcomes:</p>

Tumour response (complete response CR, partial response PR, stable disease SD, disease progression PD); Survival

Follow up:

Median follow-up = 14 years (range: 6 months to 36 years)

Results:

Orchidectomy (n=25):

CR = 1

PR = 7

SD = 6

PD = 11

Response rate if orchidectomy was primary treatment = 37%

Response rate if orchidectomy was secondary treatment after oestrogen therapy = 17%

Median RD = 17.5 months (range: 10-130 months)

Median survival from diagnosis in responders = 92 months

Median survival from diagnosis in non-responders = 33 months P <0.01

Median survival from first evidence of metastasis in responders = 42 months

Median survival from first evidence of metastasis in non-responders = 16 months P = 0.002

Oestrogens (n=18 trials):

CR = 0

PR = 3

SD = 2

PD = 13

Response rate if not previously treated with endocrine therapy = 25%

Response rate if oestrogen was secondary treatment = 0%

Median RD in previously untreated patients = 9 months

Corticosteroids (n=14 trials)

CR = 1 (primary therapy)

PR = 5 (given as salvage therapy)

SD = 3

PD = 5

Median RD = 11 months (range: 3-22 months)

Median survival from diagnosis in responders = 50 months

Median survival from diagnosis in non-responders = 42 months

Median survival from first evidence of metastasis in responders = 39 months

Median survival from first evidence of metastasis in non-responders = 30 months

Androgens (n=5 trials):

CR = 0

PR = 3

SD = 0

PD = 2

Response rate as a primary therapy = 20%

Response rate if oestrogen was secondary treatment = 40%

Tamoxifen (n=8 trials)

CR = 2 (non-orchidectomised patients)

PR = 0

SD = 3

PD = 3

Median RD of one CR (in lymph nodes) = 16 months

Median RD of other CR (in chest wall, lymph nodes & contralateral breast) = 48 months.

General comments:

This paper presented retrospective data for all men with breast cancer treated at a single US institution between 1945 and 1980. 25 patients received orchidectomy, 45 men received additive endocrine therapy (18 with oestrogens, 14 with corticosteroids, 5 with androgens and 8 with tamoxifen citrate). Endocrine receptor status was not available on these patients.

Examination of data across all the studies led the authors to correlate the length of the disease-free interval (DFI) in patients with disease progression and the response to endocrine therapy. They conclude that such therapy would be useful for men with a DFI >12 months (response rate = 59%) compared with DFI <12 months (response rate = 9% P=0.01) but added that endocrine therapy not would not significantly extend the interval between the occurrence of metastases and death, as is the case with many female breast cancers.

There are several treatment modalities examined here and some of the sub-groups i.e. tamoxifen (n=8), androgens (n=5) are too small to make any reasonable conclusions from their data.

Lopez <i>et al.</i> (1985a)
Design: Retrospective case series (therapy), evidence level: 3 Country: Italy
Inclusion criteria: Men with recurrent or progressive breast cancer Life expectancy >2 months Clearly measurable disease.
Exclusion criteria: No anti-cancer therapy in the previous month.
Population: Number of patients = 14, age range: 29 to 79 years. Mean age: 61 years
Interventions: Cyproterone acetate (CPA) (n=11 trials) Tamoxifen (n=7 trials) Oestrogens (n=5 trials) Aminoglutethimide (n=5 trials) HD-medroxyprogesterone acetate (n=3) Androgens (n=1 trial) Orchidectomy (n=3 trials)
Outcomes: Tumour response (complete response CR, partial response PR, stable disease SD, disease progression PD), response duration RD, adverse events.
Follow up: Baseline investigations included history, physical examination, KPS, complete blood cell and platelet counts, serum chemistry, X-rays, bone scans and liver scans. Only one patient received an endocrine status check.
Results: Of 14 patients, 11 had one or more treatments: 2 (n=5), 3 (n=3), 4 (n=2) and 5 (n=1) CPA: CR = 2/11, PR = 5/11, SD = 4/11 Tamoxifen: CR = 2/7, PR = 1/7, PD = 4/7 Oestrogens: CR = 1/5, PR = 1/5, PD = 3/5 Aminoglutethimide: CR = 1/5, PR = 1/5, PD = 3/5 HD-medroxyprogesterone acetate: PD = 3/3 Androgens: PD = 1/1

Orchiectomy: PR = 1/3, PD = 2/3

Median response rate for men receiving tamoxifen = 17 months.

Median response duration for men receiving CPA = 8 months.

Overall response rate for all therapies = 43%

Overall response rate for additive therapies = 44%

Median overall RD = 10 months

Median overall RD for additive therapies = 11 months

Median overall RD for men with CR or PR = 23.5 months

Median overall RD for men with SD or PD = 11 months

Adverse events:

Sexual impotence, one case of weight gain, one case of tiredness and gynaecomastia (CPA group), one case of hot flushes and mild gynaecomastia (TAM group) and somnolence (all men in the aminoglutethimide group).

General comments:

This paper presented retrospective data for all men with breast cancer treated at a single Italian institution between 1971 and 1984. Patients received a variety of interventions including surgery. The patient number overall was low and the numbers of men receiving each treatments type, obviously, even lower hence no statistics were presented or would have been valid.

The authors presented the overall response to endocrine therapy as 43-44% but no single treatment was selected as being better than the others for the reasons given. The disease-free interval was not prognostic for tumour response as has been reported in other studies. With one exception, men who had responded previously to an endocrine therapy responded further and those who had not responded the first time failed to respond subsequently.

Harris *et al.* (1986)

Design: Retrospective case series (therapy), evidence level: 3

Country: UK

Inclusion criteria:

Men with advanced breast cancer.

Exclusion criteria:

None stated

Population:

Number of patients = 5, age range: 35 to 79 years. Mean age: 56 years

Interventions:

Aminoglutethimide was given at 250 mg four times per day (or 125 mg per day in one case) all with 20 mg twice daily of replacement hydrocortisone.

Outcomes:

Tumour response.

Follow up:

None detailed

Results:

Only one patient had previously been orchidectomised and he responded to aminoglutethimide for 14 months, showing significant reductions in basal levels of oestrogens. The other four men did not experience a reduction of oestrogens or a tumour response but this was apparently not due to intrinsic hormone resistance since three of them subsequently responded well to

tamoxifen (no further details were given).

The lower dose of aminoglutethimide reduced hormone levels to the same extent as the full dose.

General comments:

This paper presented data from a very small number (n=5) of men with breast cancer, one of whom had been previously orchidectomised and given adjuvant chemotherapy (without a sustained response). Although a very small series, the authors concluded that this therapy may not be suitable for intact males but could follow orchidectomy and that tamoxifen would be a suitable first line therapy in men not previously orchidectomised.

Patel *et al.* (1984)

Design: Retrospective case series (therapy), evidence level: 3

Country: USA

Inclusion criteria:

Men with metastatic breast cancer.

Exclusion criteria:

None stated

Population:

Number of patients = 22, age range: 44 to 79 years. Mean age: 62 years

Interventions:

Bilateral orchidectomy (all patients) then aminoglutethimide & bilateral adrenalectomy (n=1) or hypophysectomy (n=1), bilateral adrenalectomy (n=10) & tamoxifen (n=3).

Outcomes:

Tumour response.

Follow up:

Two patients died post-operatively (one post hypophysectomy and one post orchidectomy).

Results:

Bilateral orchidectomy:

Objective remission = 11/22 (50%)

Mean duration of response = 15 months (range: 4-46 months)

Bilateral adrenalectomy given on disease progression or recurrence:

Objective remission = 8/10 (80%). 5 of these responders had also responded to orchidectomy.

Mean duration of response = 15 months (range: 4-40 months)

Tamoxifen given after relapse following bilateral adrenalectomy:

Objective remission = 3/3 (100%). All of these men had responded to adrenalectomy and 2 had previously responded to orchidectomy.

Mean duration of response = 9 months (range: 5-12 months).

Aminoglutethimide given after failure of orchidectomy:

Objective remission = 1/1 (100%). This patient then underwent adrenalectomy on relapse with a further remission for 6 months.

Duration of response = 7 months.

The response rates were said to be similar regardless of the location of metastases i.e. osseous, soft tissue or viscera.

Of the three ER +ve patients, two had remission after orchidectomy, two responded to

adrenalectomy and all three responded to tamoxifen.
<p>General comments: This paper presents data from the case files of 22 men treated for metastatic breast cancer at a single US centre between June 1958 and June 1982. All patients had initially been orchidectomised, after which one man received aminoglutethimide. This man and ten others subsequently received bilateral adrenalectomy after which three were given tamoxifen. Three men were tested for endocrine status.</p> <p>The authors commented that hormonal therapy was effective in those men who had previously failed to respond to such manipulation. At this point in time, endocrine status was not known to be correlated with a response to endocrine therapy.</p>

Lopez <i>et al.</i> (1985b)
<p>Design: Retrospective case series (therapy), evidence level: 3 Country: Italy</p>
<p>Inclusion criteria: Men with recurrent or progressive breast cancer Life expectancy of >2 months Clearly measurable disease</p>
<p>Exclusion criteria: Previous anti-cancer therapy within 1 month</p>
<p>Population: Number of patients = 10, age range: 42 to 77 years. Mean age: 62 years</p>
<p>Interventions: Cyproterone acetate (CPA) at 100 mg twice per day.</p>
<p>Outcomes: Tumour response (complete response CR, partial response PR, stable disease SD, progressive disease PD), response duration (RD), survival.</p>
<p>Follow up: Baseline tests included history, physical examination, KPS assessment, complete blood cell and platelet counts, serum chemistry tests, X-rays, bone scans and liver ultrasound. Endocrine receptor status was not measured. In several patients (pituitary, reproductive and thyroid) hormone levels were determined by radioimmunoassay and these tests were repeated after the study.</p>
<p>Results: Efficacy (n=10): CR = 2/10 (20%) PR = 5/10 (50%) Objective remission = 7/10 (70%) SD = 3/10 (30%) Median RD = 8 months (range: 3+ -52 months) Median RD for patients with SD = 4 months.</p> <p>In one patient, complete remission of liver, lung, bone and soft tissue disease was observed and maintained for 52 months after which time and after relapse he was given tamoxifen which further extended disease-free survival by 40 months. Most other patients had bone-only disease. No factors were identified that could accurately predict response to treatment, including measured hormone levels which varied in response to CPA but did not differ between responders and non-responders.</p>

The adverse events reported related mainly to sexual impotence, due to the anti-androgenic action of the drug, one report of gynaecomastia & tiredness and another of weight gain.

General comments:

This paper presented the results from a very small case series (n=10) of men with advanced breast cancer and mainly bone-only metastases. All had undergone mastectomy from between 12 and 141 months previously and had received adjuvant therapies including radiotherapy and/or chemotherapy. One man had also been surgically orchidectomised.

The results indicated that the response to CPA was not correlated with the decrease in testosterone levels, oestradiol or gonadotropins (NB. tamoxifen may cause an increase in these indicators and yet can result in good response levels in male patients).

Lopez *et al.* (1993)

Design: Retrospective case series (therapy), evidence level: 3

Country: Italy

Inclusion criteria:

Men with recurrent or progressive breast cancer
 Measurable or evaluable lesion
 Life expectancy >2 months
 Oral informed consent

Exclusion criteria:

Anti-cancer therapy during the four weeks prior to recruitment

Population:

Number of patients = 11, age range: 46 to 70 years. Mean age: 57 years

Interventions:

Subcutaneous buserelin at 1500 µg daily (in three equal doses) for 1 week and 600 µg daily (in three equal doses) thereafter and cyproterone acetate (CPA) at 100 mg per day starting 24 hours after the first dose of buserelin. Treatment was given until disease progression.

Outcomes:

Tumour response (complete response CR, partial response PR, stable disease SD, disease progression PD); Survival

Follow up:

Baseline tests included history, physical examination, KPS assessment, ECG, complete blood cell and platelet counts, serum chemistry tests, X-rays, bone scans, liver ultrasound and abdominal CT. Hormone (reproductive and pituitary) levels were assayed before and after the study.

Results:

Efficacy (n=11):
 CR = 2/11 (18%)
 PR= 5/11 (45%)
 Objective remission = 7/11 (63.6%)
 Median RD = 11.5 months (range: 9-24+ months)

SD = 3/11(27%)
 Median RD = 5 months with subjective remission due to alleviation of pain and improvement in PS.

PD = 1/11 (9%)

<p>Median overall survival = 18.5 months</p> <p>Adverse events: Buserelin and CPA were well tolerated but loss of libido and impotence were common. Five men experienced hot flushes and there was one report of gynaecomastia.</p>
<p>General comments: This paper describes a prospective study of 11 men admitted for treatment of breast cancer at a single Italian centre from April 1986 to publication.</p> <p>Endocrine receptor status was determined in the majority (n=8) of men. 5/8 tumours were ER +ve/PR –ve, 2/8 tumours were ER –ve/PR –ve and 1 tumour was ER –ve/PR +ve.</p> <p>Tumour responses were independent of hormone levels. The relationship between endocrine status and tumour response was not reported or discussed in the paper however, five ER +ve/PR –ve tumours responded with 1 CR and 4 PR. Two ER –ve/PR –ve tumours responded with SD or PD and the one ER –ve/PR +ve tumour responded positively to therapy (CR).</p> <p>The authors acknowledged that the low patient number in this and most similar studies precluded drawing firm conclusions about the use of androgen blockade in the treatment of male breast cancer. They recommend the combined therapy on the grounds that CPA prevented the flare response which invariably accompanied buserelin treatment.</p>

<p>Giordano <i>et al.</i> (2002)</p>
<p>Design: Retrospective case series (therapy), evidence level: 3 Country: USA</p>
<p>Inclusion criteria: Men with metastatic breast cancer.</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 5, age range: 48 to 88 years. Mean age: 71 years</p>
<p>Interventions: Anastrozole (ANA) at 1 mg per day.</p>
<p>Outcomes: Tumour response (complete response CR, partial response PR, stable disease SD, disease progression PD).</p>
<p>Follow up: No details.</p>
<p>Results: Case 1: Diagnosis: 57 years – breast mass plus one lymph node – radical mastectomy and adjuvant chemotherapy with CMF, chest wall RT and tamoxifen with RD of 5 years. Relapse: lung metastases. Treatment with aminoglutethimide with RD of 12 months. Relapse: treated with higher dose of aminoglutethimide and steroids with SD of 3 months. Relapse: 63 years - lung disease progressed. Given ANA with SD of 9 months then PD in lungs.</p> <p>Case 2: Diagnosis: 75 years – breast mass plus two lymph nodes – radical mastectomy only. RD 9 years.</p>

Relapse: axillary mass. Treatment with tamoxifen (TAM) for a CR of 1 year. Lost to follow-up for 1 year.

Relapse: treatment with tamoxifen again with a further 1 year CR.

Relapse: chest wall disease and axillary lymph nodes. Given TAM with PR of 14 months

Relapse: 88 years – chest wall metastases and axilla. Given ANA discontinued with PD after 2 months. Had multiple co-morbidities including hypertension, CHF and atrial fibrillation.

Case 3:

Diagnosis: 67 years – breast mass plus four lymph nodes – radical mastectomy and adjuvant chemotherapy with CMF, vincristine & prednisone (6 wks) and CMF (6 months) SD of 3 years.

Relapse: lung metastases. Treated with TAM with CR of 63 months

Relapse: 76 years – lung metastases. ANA therapy given but progressed throughout so discontinued after 3 months.

Case 4:

Diagnosis: 35 years – breast mass plus six lymph nodes – radical mastectomy and adjuvant CMF for 6 months, chest wall and axillary RT with RD of 7 years.

Relapse: lung metastases. Treatment with surgery and TAM. PD after 2 years.

Relapse: lung metastases. Treatment with surgery and TAM. PD after 4 years.

Relapse: 48 years – lung metastases, new disease in axilla. Treated with ANA with SD for 8 months. Discontinued after development of supraclavicular disease.

Case 5:

Diagnosis: 79 years – breast mass with no involved nodes – radical mastectomy and TAM (discontinued after 1 month due to AEs). PD after 3 years.

Relapse: lung and bone metastases. ANA therapy started but discontinued after 4 months with PD in the lungs.

General comments:

This paper reports on five men with metastatic breast cancer who received anastrozole treatment at a single US centre between 1990 and 1999. All the men were ER +ve and all but one (in whom PR status was not measured) were also PR +ve.

None of the five men treated with ANA experienced an objective response but 3/5 had temporary stabilisation of metastatic disease. Two men showed significant clinical benefit, defined as stable disease for more than 24 weeks.

El Omari-Alaoui <i>et al.</i> (2002)
Design: Retrospective case series (therapy), evidence level: 3 Country: Morocco
Inclusion criteria: Men with advanced or metastatic breast cancer.
Exclusion criteria: None stated.
Population: Number of patients = 71, age range: 32 to 97 years. Median age: 60 years
Interventions: Various
Outcomes: Epidemiology and statistics of male breast cancer.
Follow up:

Median follow-up was for 30 months (range: 3-168 months). 13 patients were lost to follow-up.

Results:

- The primary presenting symptom was a retroareolar lump (86%) with abscess (18%) and occasionally with nipple discharge (5.6%). 4% of cases had symptoms of metastatic disease
- Men were classed with T4 (52%), T3 (13%), N1 (34%) and N2 (24%) disease
- 80% were treated with radical mastectomy
- 91.5% of tumours were infiltrating ductal carcinoma (1 with Paget's disease of the nipple)
- 39 men had axillary lymph nodes with metastases. 29 men had >4 positive lymph nodes
- Only five men had endocrine status measured (four were +ve)
- Radical mastectomy was given to 48 men, modified in 7 cases
- Adjuvant chest wall and regional lymph node RT was used in 44 cases (mean dose 50 Gy)
- Tamoxifen was given to 46 men (with orchidectomy in 4)
- Adjuvant chemotherapy was given to 12 men and for palliation in 3 cases.

- Local recurrence occurred in 5 men with a median of 36 months (range: 9-156 months) delay
- 14 men developed metastases with a median delay of 12 months (range: 4-72 months) delay
- Metastases were developed in the lungs (n=5), bone (n=6), liver (n=1), liver & skin (n=1) or pleura and skin (n=1).

General comments:

This observational study presents data collected from a retrospective review of the case files of 71 men who had all been treated for breast cancer at a single Moroccan institute between 1985 and 1998. Patient characteristics, treatment and outcomes are discussed only broadly and none of the interventions are analysed for response hence this paper is of little evidential value for addressing this topic.

4.3 Combination versus sequential or single chemotherapy regimes

4.3.1 Combination vs sequential chemotherapy

Short summary

Evidence for comparing single chemotherapy with sequential chemotherapy comprised five RCTs (Creech *et al.*, 1979, Chlebowski *et al.*, 1979, Sledge *et al.*, 2003, Smalley *et al.*, 1976 and Baker *et al.*, 1974) and one observational study (Chlebowski *et al.*, 1989). The older studies were not always very stringently reported.

Two small, poor quality trials found no significant difference in tumour response, response duration, time to progression or overall survival when chemotherapy agents were given together or sequentially (on disease progression). Two other studies and a retrospective analysis of their data showed that whilst combined therapy resulted in superior tumour response and apparently significantly longer median overall survival, follow-up revealed that long term survival was no different between study arms.

One large RCT demonstrated that combining anthracycline and taxane, rather than giving the drugs sequentially in either order, resulted in a better tumour response and superior time to progression but did not improve median overall survival.

Consistently, adverse events due to combined therapy were reported as being more numerous or of greater severity than those experienced with single agents.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with metastatic breast cancer receiving chemotherapy	<ul style="list-style-type: none"> • Docetaxel • Paclitaxel • Vinorelbine • Capecitabine • Gemcitabine • Epirubicin • Adriamycin • Cyclophosphamide • Methotrexate • 5-fluorouracil • Mitozantrone • Mitomycin C 	Same agents in combination vs sequentially	<ul style="list-style-type: none"> • Time to progression • Overall survival • Response rate • Toxicity

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

The majority of papers identified from keywords report studies that assess the benefits of single drug interventions when compared with drug combinations e.g. drug A versus drugs A+B (but do not assess the impact of drug A followed by drug B at disease progression versus drugs A+B). These studies often have no control over subsequent treatment given after removal from study and so take the therapy under examination out of the context of the whole patient pathway. These papers are therefore excluded (including the very good Cochrane systematic review by Carrick *et al.* (2005) 'Single Agent versus Combination Chemotherapy for Metastatic Breast Cancer').

The remaining evidence base consists of five RCTs and one observational study. The studies in themselves are not bad in design but rather less than stringent in reporting the statistical analyses, randomisation and other features that are expected of more contemporary studies. Because the lack of such information carries with it the possibilities of introduced bias they are graded 1- or 1. A brief summary of outcomes are shown in table 4.3.1.1 below.

Study	S/C	Median OS/months (or as shown)	Median TTP or TTF/ months (or as shown)	ORR/%	Median RD/months (or as shown)
Chlebowski <i>et al.</i> , 1979	S	All = 11.4 with liver mets = 8	NR	All = 32	7.7
	C	All = 14.8 with liver mets = 15.2	NR	All = 56	13.4
Creech <i>et al.</i> , 1979	S	Responders = 19 CMF+A responders = 17 All stable = 12 CMF+A stable = 9 Disease progression = 3	Responders = 12 CMF+A responders = 10 All stable = 4 CMF+A stable = 4	All = 49 CMF+A = 12	NR

		CMF+A progression = 3			
	C	Responders = 18 Stable = 12 Disease progression = 8	Responders = 12 Stable = 5	All = 62	NR
Sledge <i>et al.</i> , 2003	S	A>T = 19.1 T>A = 22.5	A>T = 6 T>A = 6.3	A>T = 36 T>A = 34	NR
	C	22.4	8.2	47	NR
Smalley <i>et al.</i> , 1976	S	24 wks	NR	18	NR
	C	A = 48 wks B = 48 wks	A = 46 wks B = 27 wks	NR	A = 28 wks B = 34 wks
Baker <i>et al.</i> , 1974*	S	All = 10.2 Responders = 17.7	NR	5'-FU = 33 CYC = 40 VIN = 0	12.7
	C	All = 8.6 Responders = 11.3	NR	All = 43.5	NR

Table 4.3.1.1 *Reported mean values, not median. P values not shown for simplicity (please see individual studies for statistical significance of results). Abbreviations: NR not reported S/C sequential or combined A anthracycline T taxane CMF cyclophosphamide methotrexate and 5-fluorouracil CYC cyclophosphamide VIN vinorelbine PR partial response CR complete response

Baker *et al.* (1974) reported a small RCT comparing combined therapy of 5'-fluorouracil (5'-FU) cyclophosphamide, and vincristine with the same agents given sequentially on disease progression. The quality of the paper was poor for several reasons most of which relate to the likelihood of bias in, for example, the allocation of patients or the lack of an intent to treat analysis (although some patients' data had been excluded from the results due to death from toxicity). The authors reported that there were no significant differences between the two regimes with respect to tumour response, the duration of that response or of mean survival. Unfortunately these conclusions were not supported with statistical evidence. Since patients in the combination arm had a higher incidence of visceral disease and so perhaps a poorer prognosis, the outcomes of combined treatment may possibly have been undervalued in this trial.

Creech *et al.* (1979) presented a small RCT of patients randomised to receive four chemotherapeutic drugs in combination (5'-fluorouracil (5'-FU) cyclophosphamide, methotrexate and adriamycin – CAMF) or four of the drugs (CMF) in combination with the fifth (adriamycin - A) given on disease progression. For the purposes of analysis the patients were also stratified into high and low risk categories according to ambulatory status, symptoms and degree of visceral disease. The tumour response was not significantly different between arms or between high and low risk groups in either arm. The statistics in support of these findings were not reported. For those patients responding to therapy in either treatment arm, there was no significant difference in time to disease progression or in median overall survival between the CAMF and CMF + A responders. Outcomes were unsurprising since it was found that patients who responded to treatment or who were stable survived for longer than patients who failed to respond and patients in high risk groups had poorer survival than low risk patients, regardless of treatment arm. The main conclusion was that the side effects outweighed the advantages, if any of combined therapy with adriamycin but that this drug would be better left as a response to treating disease progression after initial therapy.

Sledge *et al.* (2003) provides the only recent publication relating to this question. The RCT was substantial (n = 731) in size and patients were randomised into three groups receiving either

doxorubicin and paclitaxel together (A+T) doxorubicin until progression then paclitaxel (A) or paclitaxel until disease progression then doxorubicin (T). Unfortunately the randomisation method was not discussed which means that bias cannot be excluded thus downgrading the quality of the paper to some degree and data were not well presented but, in other respects, the study appears to have been thorough. The tumour response rate and the time to treatment failure were statistically significantly lower between either of the sequential arms when compared with the combined therapy but did not differ from each other. There were no significant differences between the length of overall survival between arms, however some of the treatment-related effects appear to have been more severe in the combination arm and the authors point this factor out in their summary. They conclude that adverse events affecting the quality of life of patients have to be carefully balanced against any apparent advantage in the tumour response, particularly since the overall survival appears not to be enhanced by combining the chemotherapy agents.

Smalley *et al.* (1976) and Chlebowski *et al.* (1979) conducted very similar trials testing five-drug combinations against the same drugs in sequence each given on disease progression. The studies differ in their choice of fifth drug, either triiodothyronine or vincristine, but the other four drugs are the same (5'-FU, cyclophosphamide, methotrexate and prednisone). Smalley tried two methods of combining therapy, either as a continuous administration or by giving the treatment intermittently within a 28-day cycle, and found that the continuous administration of combined therapy resulted in a significantly higher tumour response rate than that experienced by patients in the sequential arm. Additionally the combined therapy group had a much higher median survival rate and at this point the study was closed to recruitment, presumably on ethical grounds. The authors recommended combination therapy despite finding that overall survival was not significantly different between combination and sequential treatment.

Chlebowski *et al.* (1979) used a life table analysis to find the projected survival outcomes for their treatment groups. Given the statistically superior tumour response rate and response duration for the combination therapy, it was predicted that this regime would provide a significantly better overall survival, especially for patients with a poorer prognosis. However, analysis of the full patient data showed that there was no significant difference in survival between the arms. Chlebowski *et al.* (1989) returned to this and another (Smalley *et al.*, 1976) study and combined the data for all 222 patients. As the two RCTs were very similar in patient demographics and interventions this seems to be a valid exercise. It was found that there was no significant difference in overall survival between the 129 patients treated with combination therapy and the 93 patients treated with sequential therapy. There was also no significant difference in overall survival for patients without liver metastases (64%) or without liver or lung metastases (30%) between the two arms. However, patients with liver metastases (36%) had statistically longer survival with combination treatment ($P < 0.05$).

Both trials individually reported better tumour response and time to progression data and the studies have since been interpreted to indicate that combination therapy is superior to single agents taken sequentially. The authors say, however, that whilst this might be true for the sub-set of patients with liver involvement it is probably not true for the majority of other MBC patients. They also point out that chemotherapy-related deaths were three times higher with combination therapy and that such toxicity, as well as affecting the quality of life of patients in the interim might also affect longer term survival of those who had made initially good responses.

Some of these data illustrate a limitation of the randomised controlled trials offering evidence for this question. Two sub-sets of patients were identified that either died very quickly soon after entering a study or who survived well beyond the study end. It could be argued that neither group were affected by their treatment allocation hence only about half the patients in a trial were properly testing the interventions. Since these patients occupy the middle section of a survival curve, they will contribute to the median values. If patients aren't completely and fully followed up to the end of their lives the survival analysis can over estimate the value of an intervention or exaggerate the difference between two interventions. This explains why, on further examination,

overall survival does not differ in the long run between combination and sequential therapy but only in the short duration of the study and follow-up which may be taken out of context of the patient pathway. The more aggressive combined treatment with associated side effects would seem only to favour patients with a very poor prognosis and heavy tumour burden.

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Evidence tables

Question: Sequential or combination chemotherapy for improved outcomes?
Created by: Karen Francis on 06/06/2007

Chlebowski <i>et al.</i> (1979)
Design: Randomized controlled trial (therapy) evidence level: 1 Country: United States
Inclusion criteria: Histologically confirmed MBC with measurable disease No prior cytotoxic chemotherapy No response to endocrine therapy Rapidly progressing disease
Exclusion criteria: Evidence of severe renal or liver impairment (parameters given)
Population: Number of patients = 121
Interventions:

Combination arm - 2 week cycle (n = 61):
Cyclophosphamide at 2 mg per kg daily by mouth
5'-FU at 15 mg per kg on day 1 i.v.
Methotrexate at 30 mg per m² on day 8 i.v.
Prednisone at 0.5 mg per kg daily by mouth
Triiodothyronine at 0.005 mg daily

Sequential arm (n = 60):

Drugs were given as single agents at the same dosages as above and treatment was switched on disease progression after initial response or after 4 weeks if no response occurred.

5'-FU was given for a minimum of 4 weeks followed by cyclophosphamide similarly for a minimum of 4 weeks, then triiodothyronine with prednisone for a minimum of 6 weeks and then methotrexate for a minimum of 4 weeks.

Outcomes:

Tumour response (ORR = CR + PR) complete response (CR) partial response (PR) overall survival (OS) response duration (RD) adverse events

Follow up:

Baseline assessments included physical examination, chest X-ray, bone X-ray, liver scans, bone marrow aspiration and/or biopsy, ECG, routine biochemical and haematological tests.

All patients were followed until death. 5 patients originally entered on the trial were ineligible because they had received endocrine therapy at the time of study entry.

5 patients in the sequential arm broke protocol by not receiving cyclophosphamide as their 2nd drug. These patients were censored in the survival analysis but included in the analyses for toxicity and response.

Results:

Median OS:

Combination arm = 14.8 months

Sequential arm = 11.4 months

Analysis of projected survival 12 months after entry of the last patient (and after the death of 51 patients) showed a significant difference between arms. However, life table analysis found NSD between the arms when real patient survival data were applied.

Median OS for patients with liver metastases:

Combination arm (n = 29) = 15.2 months (P < 0.04)

Sequential arm (n = 22) = 8 months

The majority of patients without liver metastases did not differ significantly from one another between arms for any time period.

ORR:

Combination arm (n = 61): CR (n = 9) + PR (n = 25) = 56%

Sequential arm (n = 60): CR (n = 2) + PR (n = 19) = 32%

Individual drugs on sequential arm:

5'-FU (n = 60): CR (n = 2) + PR (n = 12) = 23%

Cyclophosphamide (n = 46): PR (n = 5) = 9%

Triiodothyronine + prednisone (n = 34): PR (n = 1) = 3%

Methotrexate (n = 24): PR (n = 1) = 4%

Median RD:

Combination arm: 13.4 months

Sequential arm: 7.7 months (P < 0.01)

<p>Median RD for patients achieving CR or PR: Combination arm: 18 months Sequential arm: 17.6 months (NSD)</p> <p>Adverse events (all grades): Combination arm: Leukopenia (n = 42) Thrombopenia (n = 12) Nausea and vomiting (n = 33) Stomatitis (n = 7)</p> <p>Sequential arm: Leukopenia (n = 22) Thrombopenia (n = 7) Nausea and vomiting (n = 30) Stomatitis (n = 2).</p> <p>There were 2 treatment related deaths, both of which occurred in the combination arm.</p>
<p>General comments: This paper describes a study in which the aim was to see if a regimen of 5 drugs taken sequentially at the time of treatment failure would prolong the survival of patients with MBC when compared to the same 5 drugs given as a concurrent combination. Patients were recruited between February 1971 and November 1973.</p> <p>Patients were randomly assigned to one of two arms by Statistical Analysis Centre - the methodology is not given.</p> <p>Baseline demographics were similar between arms for the number of metastatic sites, disease-free interval and menopausal status (no statistics were shown). Subsequent post-study treatment was recorded and was found to be similar in both arms (details given).</p> <p>The response frequency and duration was higher for patients taking the combination therapy. In terms of survival, the authors conclude that combination therapy was of more use to patients with life threatening disease in other areas of the body but that otherwise there was no significant difference between arms.</p> <p>Survival analysis would tend to project a better outcome for patients on combination therapy because of the more immediate and superior tumour response but, as this study suggests, following all participants to the end of their lives, the survival advantages are not apparently greater over the longer term.</p> <p>As a RCT the reporting of the findings is of only moderate quality but the study was probably thorough and well conducted.</p>

Baker <i>et al.</i> (1974)
<p>Design: Randomized controlled trial (therapy) evidence level: 1- Country: United States</p>
<p>Inclusion criteria: Refractory to endocrine therapy Life threatening disease Histologically confirmed MBC</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 89</p>
<p>Interventions: Combination arm (28-day cycle n = 52):</p>

5'-FU at 7.5 mg per kg i.v. on days 1-5
Cyclophosphamide at 4 mg per kg i.v. on days 1-5
Vincristine at 0.015 mg per kg i.v. on days 1 and 8
Treatment was continued unless adverse events were not manageable

Sequential arm (n = 37):

5'-FU at 15 mg per kg i.v. on days 1-5 of a 28-day cycle
Cyclophosphamide at 8 mg per kg i.v. on days 1-5 of a 28-day cycle
Vincristine at 0.02 mg per kg i.v. weekly
Each drug was given until disease progression

Outcomes:

Tumour response (ORR = CR + PR) complete response (CR) partial response (PR) overall survival (OS) response duration (RD) adverse events

Follow up:

6 patients in the combination arm died within 30 days of study onset, all from disease progression. Similarly, in the sequential arm, 7 patients died within 30 days but 3 of these died from toxicity and 3 others experienced severe toxicity. All these patients were excluded from the results since they were deemed not to have received sufficient treatment.

Results:

Median age:

Sequential arm: 54 years (range: 26-77)

Combination arm: 52.5 years (range: 28-72)

Tumour response:

Combination arm (n = 46): CR = 2 PR = 18 (ORR = 43.5%)

Sequential arm 5'-FU (n = 30): PR = 33%

Sequential arm cyclophosphamide (n = 25): PR = 40%

Sequential arm vincristine (n = 12) = 0%

Mean survival:

Combination arm (all) = 8.6 months

Combination arm responders (n = 20) = 11.25 months

Combination arm non-responders (n = 25) = 6.7 months

Sequential arm (?all) = 10.2 months

Sequential arm responders (2 drugs) (n = 3) = 17.7 months

Mean response duration:

Sequential arm (5'-FU) = 7 months

Sequential arm (Cyclophosphamide) = 5 months

Responders sequential arm (2 drugs) (n = 3) = 12.7 months

Adverse events (moderate/severe/fatal):

Combined arm n (%):

Leukopenia = 33 (63.5%)

Thrombocytopenia = 7 (13.5%)

Neurotoxicity = 11 (21.1%)

Adverse events (moderate/severe/fatal):

Sequential arm n(%):

5'-FU: Leukopenia = 31 (83.8%) thrombocytopenia = 11 (29.7%)

Cyclophosphamide: Leukopenia = 18 (72%) thrombocytopenia = 4 (16%)

Vincristine: Leukopenia = 2 (16.6%) thrombocytopenia = 1 (8.3%) neurotoxicity = 10 (83.3%)

General comments:

This paper presents results from a small RCT of 89 women randomised to receive three chemotherapy drugs either sequentially or in combination. The participants were recruited between October 1969 and March 1971 at several oncology centres in the USA.

The method of randomisation was by means of the last digit of the admission number, despite the fact that the patient's physician could be aware of allocation. As the authors suggest, this may account for the disproportionate numbers in the two arms. It is not possible to state which outcome, if any, the resulting bias would favour.

The combination arm had a higher number of patients that had metastatic visceral involvement which may have adversely affected their survival outcome and therefore underestimated the efficacy of the regime. The authors state that differences between arms were not significant but no statistics were reported.

Authors state that overall the combination treatment produced a milder toxic effect. Although the dosages are not discussed, those of 5'-FU and cyclophosphamide are double those of the drugs administered to patients in the sequential arm which presumably contributed toward the higher number of adverse events reported.

This is not a good paper from the point that there are no details of randomisation or allocation and no statistical analyses of the results data. The report suggests, but cannot prove, that there were no differences in overall survival, response duration or treatment duration between the two arms.

Creech *et al.* (1979)

Design: Randomized controlled trial (therapy) evidence level: 1-
Country: United States

Inclusion criteria:

Not previously treated with chemotherapy
Measurable or clearly evaluable MBC
Hormone resistant disease
Progressive visceral disease
Written informed consent

Exclusion criteria:

None

Population:

Number of patients = 78, median age = 56 years

Interventions:

Patients were stratified by risk where low risk patients were ambulatory, minimally symptomatic and had no life threatening visceral disease. Patients at high risk were those that were non-ambulatory, symptomatic and had life threatening visceral disease.

Combined arm (CAMF) (28-day cycles) (n = 39):
Cyclophosphamide at 50 mg per m² on days 1-14 orally
Adriamycin at 20 mg per m² on days 1 and 8 i.v.
Methotrexate at 20 mg per m² i.v. on days 1 and 8 i.v.
5'-FU at 300 mg per m² on days 1 and 8 i.v.

Sequential arm (CMF) (28-day cycles) (n = 39):
Cyclophosphamide at 50 mg per m² on days 1-14 orally
Methotrexate at 20 mg per m² i.v. on days 1 and 8 i.v.

5'-FU at 300 mg per m² on days 1 and 8 i.v.
then on disease progression
Adriamycin at 20 mg per m² on days 1 and 8 i.v.

Outcomes:

Tumour response (ORR = CR + PR) complete response (CR) partial response (PR) overall survival (OS) stable disease (SD) progressive disease (PD) time to progression (TTP) adverse events

Follow up:

Baseline evaluation of disease extent included histological confirmation of metastatic disease, complete blood count, liver function tests, blood urea nitrogen, blood sugar, chest X-ray, bone scan and liver scan plus bone survey, bone marrow biopsy and brain scan where indicated.

Blood counts were repeated prior to each i.v. injection of chemotherapy. Extent of disease was evaluated monthly and chest X-rays and liver function tests were repeated every three months.

Results:

Tumour response combined arm (CAMF) n (%):

Low risk CR + PR (n = 20) = 13 (65%)

High risk CR + PR (n = 19) = 11 (58%)

Total CR + PR (n = 39) = 24 (62%)

Low risk SD = 6 (30%)

High risk SD = 3 (16%)

Total SD = 9 (23%)

Low risk PD = 1 (5%)

High risk PD = 5 (26%)

Total PD = 6 (15%)

Tumour response sequential arm (CMF) n (%):

Low risk CR + PR (n = 18) = 12 (67%)

High risk CR + PR (n = 21) = 7 (34%)

Total CR + PR (n = 39) = 19 (49%)

CMF+ Adriamycin (n = 25) PR = 3 (12%)

Low risk SD = 5 (28%)

High risk SD = 7 (33%)

Total SD = 12 (31%)

CMF + Adriamycin SD = 9 (36%)

Low risk PD = 1 (5%)

High risk PD = 7 (33%)

Total PD = 8 (20%)

CMF + Adriamycin PD = 13 (52%)

There was NSD in tumour response between CMF and CAMF arms. There was also NSD in tumour response between high and low risk patients in either treatment arm.

Median TTP combination arm (CAMF):

Low risk responder (n = 20) = 11 months

High risk responder (n = 19) = 15 months

Total responder (n = 39) = 12 months

Low risk SD = 10 months

High risk SD = 4.5 months

Total SD = 5 months

Median TTP sequential arm (CMF):

Low risk responder (n = 18) = 12 months

High risk responder (n = 21) = 12 months

CMF + Adriamycin responder (n = 25) = 10 months

Total responder (n = 39) = 12 months

Low risk SD = 4.5 months

High risk SD = 4 months

CMF + Adriamycin SD = 5 months

Total non-responder = 4 months

There was NSD in median TTP between CMF and CAMF responders.

Median OS combination arm (CAMF):

Low risk responder (n = 20) = 18 months

High risk responder (n = 19) = 22 months

Total responder = 18 months

Low risk SD = 12 months

High risk SD = 3 months

Total SD = 12 months

Low risk PD = 8 months

High risk PD = 3 months

Total PD = 8 months

Median OS sequential arm (CMF):

Low risk responder (n = 18) = 24 months

High risk responder (n = 21) = 17 months

CMF + Adriamycin responder (n = 25) = 17 months

Total responder = 19 months

Low risk SD = 12 months

High risk SD = 7 months

CMF + Adriamycin SD = 9 months

Total SD = 12 months

Low risk PD = 19+ months

High risk PD = 3 months

CMF + Adriamycin PD = 3 months

Total PD = 3 months

There was NSD in median OS between CMF+A and CAMF responders.

Adverse events:

Combined arm (CAMF):

WBC < 3000 = 54%

Vomiting = 18%

Alopecia = 77%

Local tissue damage = 10%

Sequential arm (CMF only):

WBC < 3000 = 23% (P = 0.007)

Vomiting = 0% ((P = 0.01)
Alopecia = 0% P < 0.0001)

Sequential arm (CMF + A):
WBC < 3000 = 12%
Vomiting = 12%
Alopecia = 40%

General comments:

This paper presents a RCT of combined treatment with four chemotherapeutic drugs versus three of these drugs in combination with the fourth (adriamycin) given at disease progression. There are no details of randomisation. Patients were stratified by risk.

Actuarial survival and response duration were analysed using life tables and the resulting probability curves were compared after the method of Thomas and Grunkemeier.

Patients in two arms were stated to be similar in respect of characteristics which included prior therapy, risk status, age and disease-free interval (no statistics were presented). Patients who had a positive response to therapy or who had stable disease had better survivals than patients with progressive disease. This was true in both treatment arms. Patients who were in the poor risk group had lower median survival times than patients in the low risk groups. This was true in both treatment arms.

Chemotherapy-induced partial responses of a high risk patient positively influenced survival.

Only 25/39 patients in the sequential therapy arm were able to receive the treatment with adriamycin on disease progression. The remaining 14 patients either had terminal disease (n = 8) did not have progressive disease (n = 4) or were lost to follow-up before receiving an adequate trial of adriamycin. The data are presented as an intention to treat analysis and also with this CMF + adriamycin sub-group only.

Authors suggest that a low dose CMF with minimal toxicity is as effective a treatment as the combination with adriamycin which has much higher toxicity and that this more potent drug might be better given on disease progression.

Sledge *et al.* (2003)

Design: Randomized controlled trial (therapy) evidence level: 1-
Country: United States

Inclusion criteria:

Histologically confirmed breast cancer with progressing regional or metastatic disease
Prior (> 6 months previously) non-anthracycline or non-taxane adjuvant therapy was acceptable
Prior endocrine therapy in any setting was acceptable
Measurable or evaluable disease (defined by ECOG) including pleural or peritoneal effusions
Adequate renal, haematological and hepatocellular function
ECOG status of 0,1 or 2
Life expectancy > 3 months

Exclusion criteria:

History of congestive heart failure
Myocardial infarction within 6 months
Ischemic heart disease requiring medication
Cardiac conduction abnormalities
Receipt of drugs known to affect cardiac conduction
History of deep vein thrombophlebitis

<p>Any other thromboembolic conditions Prior malignancy < 5 years except CIS cervix or non-melanoma skin cancer No RT except to breast, chest wall or to < 25% bone marrow</p>
<p>Population: Number of patients = 731</p>
<p>Interventions: Therapy was administered every three weeks as follows:</p> <p>Arm A (n = 245): Started on doxorubicin (60 mg per m²) i.v. for a maximum of 8 cycles or until progression then crossed over to paclitaxel</p> <p>Arm T (n = 242): Started on paclitaxel (175 mg per m²) over 24 hours until progression then crossed over to doxorubicin</p> <p>Arm A+T (n = 244): Combined doxorubicin (50 mg per m²) followed after 3 hours by paclitaxel (150 mg per m²) over 24 hours</p>
<p>Outcomes: Tumour response (ORR = CR + PR) complete response (CR) partial response (PR) overall survival (OS) stable disease (SD) progressive disease (PD) time to treatment failure (TTF) adverse events Quality of life (assessed by FACT-B questionnaire) Adverse events.</p>
<p>Follow up: 33 patients were excluded from the analysis: Concurrent tamoxifen (n = 2) No evaluable disease (n = 7) Adjuvant chemotherapy within 6 months (n = 1) No histological proof of MBC (n = 1) Endocrine therapy within 2 weeks (n = 8) Prior metastatic breast cancer (n = 4) Major surgery < 4 weeks prior (n = 1) Laboratory values > 2 weeks old (n = 2) Cardiac history (n = 1) Consent signed after randomisation (n = 1) Inadequate history taking (n = 4) Extensive prior RT (n = 1)</p> <p>The number of patients included in the analysis (683) differs from the total number of patients assigned (731) by 48, of which only 33 are accounted for, as above.</p>
<p>Results: Median age: Arm A (n = 224) = 58 years (range: 25 - 79 years) Arm T (n = 230) = 56 years (range: 25 - 76 years) Arm A+T (n = 229) = 56 years (range: 27 - 78 years)</p> <p>ORR: Arm A = 36% (6% CR) Arm T = 34% (3% CR) Arm A+T = 47% (9% CR) Arm A versus Arm T (NSD) Arm A versus Arm A+T (P = 0.017) Arm T versus Arm A+T (P = 0.006)</p>

Median TTF:

Arm A = 6 months

Arm T = 6.3 months

Arm A + T = 8.2 months

Arm A versus Arm T (NSD)

Arm A versus Arm A+T (P = 0.0022)

Arm T versus Arm A+T (P = 0.0567) NB. this is not significant

Median OS:

Arm A = 19.1 months

Arm T = 22.5 months

Arm A + T = 22.4 months

Arm A versus Arm T (NSD)

Arm A versus Arm A+T (NSD)

Arm T versus Arm A+T (NSD)

Adverse events:

% of patients with grade 3/4 events (Arm A)(Arm T)(Arm A+T):

Leukopenia (49.6)(59.9)(54.9)

Thrombocytopenia (5.4)(2.1)(16.0)

Anemia (6.2)(9.5)(17.2)

Infection (4.1)(8.3)(12.7)

Cardiac complications (8.7)(3.7)(8.6)

Neurologic complications (1.6)(3.7)(10.7)

Vomiting (6.6)(2.5)(4.5)

Diarrhoea (1.6)(1.6)(4.5)

Stomatitis (7.8)(2.9)(4.5)

Lethal toxicity (2.5)(1.6)(1.6)

Prognostic factors for impaired OS (Relative risk):

ER -ve (RR = 1.7, P = 0.0001)

Visceral dominant disease (RR = 1.4, P = 0.004)

>3 sites of disease (RR = 1.4, P = 0.005)

Short disease-free interval (1-24 months) (RR = 1.3, P = 0.03)

Prior systemic therapy (RR = 1.1, P = 0.03)

Treatment regime was NSD

Crossover responses:

Tumour response from Arm A to Arm B = 28/129 patients (22%)

Tumour response from Arm B to Arm A = 25/128 patients (20%)

Median TTF from Arm A to Arm B = 4.5 months

Median TTF from Arm B to Arm A = 4.2 months

Median OS from Arm A to Arm B = 14.9 months

Median OS from Arm B to Arm A = 12.7 months

All results are NSD

Quality of life (n = 451 patients completing questionnaires at both baseline and follow-up in week 16): There were no significant differences between any arms for any subscale.

General comments:

This three-arm RCT compares single agents versus the same agents in combination. Patients on either of the single agent arms crossed over to the other agent on disease progression. The 731 study participants are assumed to be women - it is not stated otherwise in the text. They were recruited between February 1993 and September 1995.

Statistical power calculations determined the number needed to detect a 15% improvement in ORR and a 50% improvement in TTF between any two arms. Doxorubicin as a single agent was assumed to have an ORR of 30-35% and a median TTF of 6-8 months. With 220 patients on each arm the actual power would have been 0.84 for the ORR and 0.95 for TTF.

The three arms were said by the authors to have been well matched in respect of patient characteristics but there is no statistical evidence to exclude heterogeneity. Appropriate statistics were used to compare tumour response rates, TTF and OS and to examine potential prognostic factors on both.

There are no details of randomisation or allocation. This means that it would be impossible to rule out the possibility of bias in the observed results. Some patients are missing from the outcomes analysis and data are poorly presented. There is no mention of an ITT analysis.

The authors concluded that:

- Combination therapy resulted in superior ORR and TTF but failed to improve OS or quality of life.
- The percentage of patients who may have responded only to one or other of the two drugs may have been the same as the number who responded to the combination anyway.
- The OS may relate more to biology of the disease since the prognostic factors point towards these indicators rather than the chemotherapy regime.
- Combination therapy often involves a reduction in the dosage of individual drugs which might compromise the likelihood of synergy between them.
- Combination therapy may impair the quality of life if the adverse events are disproportionate to the response.

Smalley *et al.* (1976)

Design: Randomized controlled trial (therapy) evidence level: 1-

Country: United States

Inclusion criteria:

Metastatic or recurrent BC

Non-measurable disease e.g. pleural effusion was acceptable

Exclusion criteria:

Premenopausal (menstruating, <50 years of age and/or with amenorrhea for <1 year) patients unless their ovaries had been removed.

Population:

Number of patients = 101

Interventions:

Arm A: combined - continuous every week (n = 35):

Methotrexate at 20 mg per m² orally

5'-FU at 400 mg per m² i.v.

Vincristine at 1 mg per m² i.v.

Cyclophosphamide at 100 mg daily orally

Prednisone at 45 mg per day for 14 days then 30 mg per day for 14 days then 15 mg per m² for 28 days orally

Arm B: combined - intermittent every 28 days (n = 33):

Methotrexate at 30 mg per m² orally on days 0 and 7

5'-FU at 400 mg per m² i.v. on days 0 and 7

Vincristine at 1 mg per m² i.v. on days 0 and 7

Cyclophosphamide at 400 mg daily i.v. on day 0
Prednisone at 20 mg 4 doses per day for 7 days orally

Arm C: sequential single agents, each until relapse (n = 34):

5'-FU at 600 mg per m² i.v.

Methotrexate at 20 mg per m² biweekly orally then...

Cyclophosphamide at 100 mg per m² orally then...

Vincristine at 1 mg per m² per week i.v. then...

Prednisone at 45 mg per day for 14 days then 30 mg per day for 14 days then 15 mg per m² for 28 days orally.

Outcomes:

Tumour response (ORR = CR + PR) complete response (CR) partial response (PR) overall survival (OS) stable disease (SD) progressive disease (PD) response duration (RD) adverse events

Follow up:

Objective response was evaluated at the 8th study week.

9 patients were dropped from due to ineligibility or protocol violation before or during the study (arm A = 5, arm B = 3, arm C = 1) leaving 101 evaluable participants.

Results:

Median age:

Arm A = 55 years (range: 26-83 years)

Arm B = 55 years (range: 34-75 years)

Arm C = 55 years (range: 28-78 years)

Tumour response:

Arm A (n = 35):

CR + PR = 16 (46%)

SD = 7

PD = 12

Arm B (n = 33):

CR + PR = 9 (27%)

SD = 11

PD = 13

Arm C (n = 34):

CR + PR = 6 (18%)

SD = 6

PD = 22

Regime A (combined) versus C (sequential) (P<0.05)

Response to individual drugs in the C arm:

5'-FU (n = 34):

Response = 6

Stable disease = 6

Progressive disease = 12

Died receiving therapy = 10

Off study = 1

Methotrexate (n = 20):

Response = 1

Stable disease = 6

Progressive disease = 5
Died receiving therapy = 8
Off study = 2

Cyclophosphamide (n = 9):
Response = 1
Stable disease¹ =
Progressive disease = 6
Died receiving therapy = 1
Off study = 2

Vincristine (n = 5):
Response = 0
Stable disease = 3
Progressive disease = 2
Died receiving therapy = 0
Off study = 0

Prednisone (n = 5):
Response = 0
Stable disease = 2
Progressive disease = 3
Died receiving therapy = 0
Off study = 0

Median response duration:
Arm A responders (n = 16) = 28 weeks (range: 4 - 78 weeks)
Arm B responders (n = 9) = 34 weeks (range: 15 - 115 weeks)
Arm C responders (n = 6) = 16 weeks (range: 6 - 98+ weeks)

Median survival:
Arm A = 48 weeks
Arm B = 48 weeks
Arm C = 24 weeks

Regimes A or B versus C (P < 0.05)

Adverse events:
Granulocytopenia < 1,500 mm³:
Arm A = 8
Arm B = 3
Arm C = 0

Granulocytopenia < 750 mm³:
Arm A = 10
Arm B = 1
Arm C = 1

Thrombocytopenia < 100,000 mm³:
Arm A = 6
Arm B = 1
Arm C = 0

Thrombocytopenia < 50,000 mm³:
Arm A = 4

Arm B = 0
Arm C = 2

Drug associated mortality:

Arm A = 3
Arm B = 3
Arm C = 2

Infection:

Arm A = 7
Arm B = 2
Arm C = 0

General comments:

This paper describes a small three-arm RCT testing 5 drug therapy sequentially, in continuous combination or in combination but given intermittently.

Patients were randomised by a centrally issued, sequentially numbered envelope method where neither the investigators nor patients knew the allocation in advance of the study. Recruitment was between October 1971 and September 1973.

Arm A had superior tumour response compared with the other two arms and median survival for arm A was twice as long as for the sequential arm. For this reason the study was closed to further recruitment when the median survival point was reached.

Continuously administered combination therapy produced a higher number of responders than sequential therapy.

About 25% of patients had sufficiently advanced disease to have not responded to any treatment (these data are at the top of a survival curve). 25% of patients had a strong response and long survival regardless of therapy and these were mainly over the age of 50 years with disease confined to local skin recurrence with or without bone metastases (these data are at the bottom of a survival curve). 50% of patients therefore were influenced by their mode of therapy. The data for these patients are found in the centre of the survival curves and this region was found to be significantly different between arms. However, when the full survival curves were later examined it was found that there was no significant difference in overall survival between the three arms (no statistics are shown in support of this conclusion).

The authors recommend combination therapy as giving the best response to the majority of patients and they also suggest prolonged survival although, beyond the median values, their data do not appear to support this finding.

Chlebowski *et al.* (1989)

Design: Observational study (therapy) evidence level: 3

Country: United States

General comments:

This paper describes a statistical data exercise which combines the results of two studies Chlebowski *et al.* (1979) and Smalley *et al.* (1976) which, according to the authors, are similar enough in all respects.

Kaplan Meier survival analyses were undertaken and comparisons made of survival between groups of patients using Cox and Peto-Mantel tests.

At the time of this report, 210 of the 222 patients had died and the length of follow-up had been as long as 143 months after study commencement.

There was no significant difference in overall survival between the 129 patients treated with combination therapy and the 93 patients treated with sequential therapy. There was also no significant difference in overall survival for patients without liver metastases (64%) or without liver or lung metastases (30%) between the two arms. However, patients with liver metastases (36%) had statistically longer survival with combination treatment ($P < 0.05$).

Both trials individually reported better tumour response and time to progression data and have since been interpreted to indicate that combination therapy was superior to single agents taken sequentially. The authors feel, however, that this might be true for the sub-set of patients with liver involvement but not for the majority of other MBC patients. They also point out that chemotherapy-related deaths were three times higher with combination therapy and that such toxicity, as well as affecting the quality of life of patients in the interim might also affect longer term survival of those who had made initially good responses.

4.3.2 Combination vs single chemotherapy

Short summary

Evidence for comparing single chemotherapy with combined chemotherapy comprised one very high quality systematic review ($n > 7,000$ study participants) (Carrick *et al.*, 2005) a more modest systematic review (Takeda *et al.*, 2007) three RCTs (Eijertsen *et al.*, Pacilio *et al.*, 2006 and Martin *et al.*, 2007) and two post-study papers published from the pivotal trial by O'Shaughnessy *et al.*, (2002) (Leonard *et al.*, 2006 and Miles *et al.*, 2004).

Good evidence suggests that the relative risk of death was significantly reduced for patients given combined chemotherapy agents compared with single drugs as first or second line treatment. The advantage was greatest for combinations which did not include their comparator. Combined therapies containing anthracyclines or alkylating agents were significantly better at reducing the relative risk of death whereas taxanes did not improve survival as part of a combined therapy.

RCT evidence from three trials showed that first line treatment with combined therapies including an anthracycline and/or taxane compared with the same anthracycline or taxane, provided no survival advantages but were associated with higher levels of adverse events. Quality of life outcomes were equivocal. Similarly, a small RCT compared second line (or higher) combined therapy of vinorelbine and gemcitabine with vinorelbine alone and reported no significant difference in overall survival between arms but more adverse events with combined therapy. In contrast, a post-study analyses of long term patient outcomes from a trial of capecitabine (CAP) and docetaxel (DOC) vs DOC alone showed that either combined or sequential therapy with the two agents was significantly better in terms of survival than receiving DOC alone.

Although considerable data were published within systematic reviews about comparison of adverse events and quality of life between combined and single agent regimes the findings were equivocal across studies.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with metastatic breast	<ul style="list-style-type: none"> (Docetaxel) 	Same agents in combination	<ul style="list-style-type: none"> Overall survival

POPULATION	INTERVENTION	COMPARISON	OUTCOME
cancer receiving chemotherapy	<ul style="list-style-type: none"> • (Paclitaxel) • (Vinorelbine) • (Capecitabine) • Gemcitabine • Epirubicin • Adriamycin • Carboplatin B 	vs singly Specific combinations; <ul style="list-style-type: none"> • Docetaxel/ Gemcitabine • Docetaxel/ Capecitabine • FEC/ FAC • Paclitaxel/ Carboplatin • Capecitabine/ Vinorelbine • Anthracycline/ Taxane • Gemcitabine/ Carboplatin 	<ul style="list-style-type: none"> • Quality of life

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

The evidence base for this topic is not extensive. One very high quality systematic review (Carrick *et al.*, 2005) examines a wide range of single versus combined therapy regimes whilst another, very limited, systematic review (Takeda *et al.*, 2007) presents findings from a (yet to be published) trial of gemcitabine (GEM) and paclitaxel (PAC) vs PAC, by extracting data from three (possibly non-peer reviewed) abstracts. Two modest quality RCTs presented data from comparisons of epirubicin (EPI) and vinorelbine (VIN) vs EPI (Eijertsen *et al.*, 2003) and GEM and VIN vs VIN (Martin *et al.*, 2007). Two further papers were published from the trial by O'Shaughnessy *et al.* (2002) of capecitabine (CAP) and docetaxel (DOC) vs DOC: Leonard *et al.* (2006) presented a retrospective analysis on the effects of within trial drug dose reductions on overall survival and Miles *et al.* (2004) published a follow-up paper reporting the influence of CAP and DOC as post-study therapies on overall survival in light of the original treatment allocation. All but two papers (Eijertsen *et al.*, 2003 and Martin *et al.*, 2007) report improved survival for combined therapies when compared to monotherapies. Both studies in which VIN was combined with another agent failed to show an advantage over a monotherapy regime and Carrick *et al.* (2005) also questioned whether or not taxanes in combination were superior to taxanes given alone.

Carrick *et al.* (2005) reviewed single vs combination chemotherapies either where the single agent also formed part of the combined therapy regime or where the comparators were completely different. The analyses comprised thirty-seven trials (with over 7,000 participants) of first and second line drugs including anthracyclines, taxanes, anti-metabolites and alkylating agents.

Across all studies, survival data were available for 86% of the randomised participants and results showed that the relative risk for patients given combined therapies was 88% of that for those patients given single drug regimes (95%CI: 0.83-0.94) ($P < 0.0001$). These results were completely unchanged when only data for those women receiving first-line therapy were analysed. Looking only at those studies comparing a single agent with a combination therapy which included that agent, the advantage of combined therapy was lower, at 91% (95%CI: 0.85-0.98) ($P = 0.02$) whilst single agents compared with combination regimes NOT including the single agent were significantly more favourable to the combined therapy, at 83% (95%CI: 0.74-0.92) ($P = 0.0003$).

Amongst the sub-analyses for drug types where the single agent was also included in the combined therapy regime, anti-metabolites in combination showed the greatest advantage over a single anti-metabolite (HR = 0.65 (95%CI: 0.50-0.86) (P = 0.003) but there was significant between trials heterogeneity which may adversely affect the soundness of these results. Combination therapies containing anthracyclines or alkylating agents were all significantly superior in terms of the relative risk (HR of 95% and 91% respectively) but taxanes were thought not to be advantageous to survival when added to a combined therapy (whether or not that combination also included a taxane).

Within this review, quality of life (QOL) was measured and reported in only nine studies using several scales assessing mainly mood, pain, nausea, vomiting, diarrhoea, hair loss, loss of appetite and social functioning. Of these, four studies reported statistically significant differences between combined and single agent therapy but with mixed findings. One trial (Heidemann *et al.*, 2002) found that patients receiving mitoxantrone (MTX) experienced less hair loss, nausea and vomiting than those on fluorouracil, EPI and cyclophosphamide (FEC). Joensuu *et al.* (1998) found that patients were less physically distressed after six months of EPI monotherapy, including less nausea than those who received FEC followed by VIN. However, Nabholz *et al.* (1999) reported that patients in the DOC arm of a trial had less nausea and vomiting but that patients in the other arm (mitomycin plus VIN) had poorer social functioning. Finally, Simes *et al.* (1994) found that patients in a combination arm (CMFP vs MTX) reported better QOL for pain, mood and nausea & vomiting over the first three months of the trial but lower QOL with regard to hair loss compared with single agent MTX.

Takeda *et al.* (2007) reviewed a trial of GEM and PAC vs PAC which is yet to be published, extracting the data from three meeting abstracts (O'Shaughnessy *et al.*, 2003, Albain *et al.*, 2004 and Moynour *et al.*, 2004). Since these reports are incomplete and may not have been peer reviewed the conclusions should be viewed with caution as the likelihood of bias is strong. With a median follow-up of 15.6 months the reported median OS for combined therapy is 18.5 months (95%CI: 16.5-21.2) and for PAC monotherapy is 15.8 months (95%CI: 14.4-17.4). Unfortunately there is no associated P-value and hence statistical significance is not known but the confidence intervals overlap suggesting non-significance of the median value but data may not be complete. Conversely, Kaplan-Meier analysis suggests a considerable survival benefit to GEM + PAC with a relative risk of 78% regardless of adjustments for baseline variation. Reports of QOL outcomes differ between the abstracts but no data were given for these preliminary findings.

Eijertsen *et al.* (2003) presents data from a phase III RCT (n = 387) comparing VIN and EPI with EPI monotherapy as first line therapy for MBC. With a fairly long follow-up of about 42 months per arm, the majority of patients in both arms had experienced disease progression. The median OS for the combined therapy was 19.1 months compared with 18 months for EPI monotherapy – although confidence intervals were not given the P-value (0.5) confirmed the lack of significant difference between treatments. Whilst QOL was not an outcome for this study, the incidence of adverse events were significantly higher with combined therapy which together with survival data caused the authors to recommend the combined therapy only in patients with rapidly progressive disease. Unfortunately, this trial failed to give details of allocation and randomisation and hence bias cannot be ruled out.

Martin *et al.* (2007) described a smaller (n = 252) trial comparing VIN and GEM with VIN monotherapy for MBC patients who had previously received anthracyclines and taxanes. Data were analysed at a point where over 80% of participants had experienced disease progression. Just over half of the patients in both study arms received the intervention as second line therapy, a third as third line therapy and the rest as first line treatment for MBC. The median OS for combined therapy was 16.4 months (95%CI: 11.6-21.1) and for monotherapy 15.9 months (95%CI: 12.6-19.1) and there was no significant difference between the two groups (P = 0.8). Quality of life was not an outcome in this trial. With a slightly increased risk of adverse events and lack of significance in improvement in survival (or disease-free progression) the authors made no recommendation for combined therapy.

In 2002, O'Shaughnessy published results from a large (n = 511) RCT of DOC and CAP compared to DOC monotherapy in which the authors found the combined therapy to be significantly superior in terms of survival. In a follow-up paper, Miles *et al.* (2004) reported on the influence of post-study treatment and showed that patients in the DOC monotherapy arm who had subsequently received single agent CAP had a survival advantage over patients receiving any other post-study therapy (median OS = 21 month (95% CI: 15.6-27.6) vs 12.3 months (95% CI: 10.5-14) a hazard ratio of 0.5 (P < 0.005). Patients originally allocated to combined therapy but who subsequently received either single agent CAP or single agent DOC showed similar survival rates: median OS 18.3 months (95%CI: 14.5-23.4) vs 15.8 months (95%CI: 9.9-21.5) P = 0.2. The authors concluded that a clear survival advantage existed for patients receiving either CAP and DOC combined therapy or sequential treatment with both agents. QOL was not reported.

Leonard *et al.* (2006) also presented a paper on data from the O'Shaughnessy trial. The authors performed a retrospective analysis looking at dose reductions within the study period and their influence on survival. Unfortunately, the relatively low numbers in this sub-group analysis weakened the findings statistically and data were only poorly presented hence this does not provide strong evidence. There was no significant difference between the median OS for patients who had received reduced drug dosage of CAP and DOC compared to those study participants who had received at least four cycles of therapy with both drugs at full dose (16.3 months compared with 13.1 months). QOL was not reported.

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Evidence tables

Question: Single vs combined chemotherapy
 Created by: Karen Francis on 29/10/2007

Ejlertsen <i>et al.</i> (2003)
Design: Randomized controlled trial (therapy) evidence level: 1- Country: Denmark
Inclusion criteria: Histologically verified MBC Between 18 and 75 years of age Progressive measurable or assessable disease with or without bone lesions WHO performance status ≤ 2 Adequate (defined) blood and laboratory parameters
Exclusion criteria: Prior or concomitant malignant disease (except BCC skin or CIS cervix) Congestive heart failure Clinical symptoms suggesting peripheral neuropathy or brain metastases Prior irradiation of > 25% bone marrow Previous anthracycline or other cytotoxic treatment for local or metastatic disease.
Population:

<p>Number of patients = 387, age range 29 to 75 years, median age = 55 years</p>
<p>Interventions: Patients were randomised to receive either:</p> <p>1] VIN + EPI (n = 193): Vinorelbine (VIN) at 25 mg per m² i.v. on days 1 and 8 with epirubicin (EPI) at 90 mg per m² i.v. on day 1 taken every 3 weeks</p> <p>2] EPI monotherapy (n = 194): EPI at 90 mg per m² i.v. on day 1 every 3 weeks</p> <p>Treatment was continued until disease progression, severe toxicity (defined) patient refusal or for a maximum of 1 year. EPI was stopped when the cumulative dose exceeded 1,000 mg per m² (reduced to 950 mg per m² from June 1999). Dose reductions of both drugs were imposed if certain haematological parameters fell below acceptable levels or in the event of febrile neutropenia.</p>
<p>Outcomes: Overall survival (OS)</p> <p>(Other outcomes included tumour response, progression-free survival, response duration and toxicity. Quality of life was not reported).</p>
<p>Follow up: Baseline investigations included full medical history, physical examination, serum chemistry, chest X-ray, MUGA scan, ECG, bone scan and other imaging modalities as appropriate. Tumour measurements made at baseline were repeated after every three treatment cycles.</p> <p>Median follow-up was 42.8 months (combined) or 41.6 months (EPI monotherapy). At the time of data analyses, 88% of combined therapy patients and 93% monotherapy patients had experienced tumour progression.</p>
<p>Results: Median OS: EPI+ VIN = 19.1 months EPI monotherapy = 18 months (NSD P = 0.5)</p> <p>Multivariate analysis of OS taking into account potential prognostic factors (stage at diagnosis, performance status, number of organs involved, visceral involvement or treatment with i.v. VIN) did increase the difference between the two arms but the median values still did not reach significance (P = 0.13).</p> <p>QOL is not reported in this paper but the incidences of leukopenia, anaemia, infection, thrombocytopenia, peripheral neuropathy and stomatitis were all significantly higher in the combined therapy arm.</p>
<p>General comments: This paper describes a multi-centre (15 oncology departments) phase III trial comparing epirubicin monotherapy with epirubicin and vinorelbine combined as first-line treatment for MBC. Patients were randomised centrally by unknown methodology and stratified by treatment centre.</p> <p>Patients were recruited between February 1995 and June 1999.</p> <p>In light of the only slight improvements in progression-free and overall survival plus the increased incidence of adverse events, the authors could only recommend combined therapy in patients with extensive and rapidly progressive disease who might not be eligible for a second line of chemotherapy.</p>

Martín <i>et al.</i> (2007)
Design: Randomized controlled trial (therapy) evidence level: 1- Country: Spain
Inclusion criteria: Histologically, locally recurrent MBC who could not be treated by surgery or RT Previous anthracyclines and taxanes Maximum 2 years previous chemotherapy At least 18 years of age WHO performance status ≤ 2 Adequate (defined) haematological, renal and liver functions Life expectancy ≥ 12 weeks Written informed consent.
Exclusion criteria: Pregnant or breast feeding Male Previous treatment with gemcitabine, vinorelbine or any other agent within 30 days of study entry Active infection, serious systemic disorder, second primary malignancy (except BCC skin or CIS cervix) Clinical evidence of brain metastases
Population: Number of patients = 252, age range 28 to 82 years, median age = 58 years
Interventions: Patients were randomised to receive either: (1) VIN + GEM (n = 125): VIN was administered at 30 mg per m ² on days 1 and 8 of a 21-day cycle, given i.v. over 6-10 min. This was followed after 30 min by gemcitabine (GEM) administered at 1200 mg per m ² given i.v. over 30 min. (2) VIN monotherapy (n = 127): vinorelbine (VIN) was administered at 30 mg per m ² on days 1 and 8 of a 21-day cycle, given i.v. over 6-10 min Treatment was discontinued on disease progression, in the interest of the patient (from the investigator's perspective) at the request of the patient or for unacceptable toxicity. G-CSF treatment was allowed in the event of febrile neutropenia, prolonged neutropenia or infection. GEM and VIN dosage modification or withdrawal was allowed in the event of unacceptable haematological or non-haematological toxicity as measured by laboratory criteria or at the discretion of the principle investigator.
Outcomes: Overall survival (OS) progression-free survival (PFS) response duration (RD) tumour response and adverse events. Quality of life was not reported.
Follow up: Baseline abdominal and thoracic CT scans or radiography, bone scans and blood tests were all performed in the four weeks before study. Blood chemistries and counts were repeated at the beginning of each treatment cycle. Blood counts were also done on day 8 of each cycle. Medical history, physical examination, performance status and tumour measurements were conducted within one week of the first treatment cycle and on the start day of each cycle thereafter. Tumour measurements were also taken every three cycles and compared with those

made at baseline.

At the point of first analysis of PFS, after 205 events, 28 patients in group 2 and 18 patients in group 1 had been censored.

Results:

VIN monotherapy: 15% patients received VIN as 1st line therapy, 54% as 2nd line therapy and 31% as 3rd line therapy

VIN + GEM: 21% patients received VIN + GEM as 1st line therapy, 52% as 2nd line therapy and 27% as 3rd line therapy

Median OS:

VIN + GEM = 16.4 months (95% CI: 11.6 - 21.1)

VIN monotherapy = 15.9 months (95% CI: 12.6 - 19.1) (NSD)

QOL was not reported but safety data showed that the commonest grade 3 or 4 toxicity was neutropenia reported in 61% of VIN + GEM patients compared with 44% of VIN monotherapy patients (P = 0.0074). Febrile neutropenia occurred in 11% patients in the VIN + GEM arm and 6% in the VIN monotherapy group (P = 0.15).

The overall incidence of grade 3 and 4 non-haematological toxic effects were similar between arms except for alkaline phosphatase (7% in VIN + GEM versus < 1% in VIN monotherapy (P = 0.009)) and vomiting (31% in VIN + GEM vs 20% in VIN monotherapy (P = 0.048)).

The increased incidence of adverse events may not have impacted significantly on QOL.

General comments:

This paper reports the final results of a phase III RCT (GEICAM 2000-04) which tests vinorelbine monotherapy against a combination therapy of gemcitabine and vinorelbine. Patients were recruited between January 2001 and March 2005 from 37 centres in 6 countries

Patients were randomised at a central point (GEICAM HQ) by means of a previously computer generated random code and were stratified by centre, number of previous treatment lines (i.e. 0, 1 or 2) and presence of visceral metastases (y or n).

The trial was conducted unblinded for reasons that were not explained. There is a likelihood of bias, therefore, since some of the researchers declared an interest in Eli Lilly, the company which manufactures gemcitabine.

Data were analysed on an intention to treat basis. Statistical analyses were appropriate. PFS was presented as Kaplan Meier survival curve.

Authors stated that 'patients were generally well balanced between groups' - there were some (probably non-significant differences) which were highlighted.

65% of patients in group 2 and 79% in group 1 were given further systemic therapy after this trial and hence the results on OS will have been considerably influenced.

Authors conclude that combination therapy provided superior only in terms of PFS but acknowledge that the influence on OS cannot be determined and that side effects are more severe with combined therapy.

Although patients were stratified by treatment centre, no discussion of this was identified.

Leonard <i>et al.</i> (2006)
Design: Randomized controlled trial (therapy) evidence level: 3 Country: Multi-centre
Inclusion criteria: Female patients \geq 18 years with histologically or cytologically confirmed breast cancer with unresectable locally advanced and/or MBC
Exclusion criteria: Previous treatment with docetaxel-containing regimen in adjuvant or advanced disease setting Previous treatment with three or more previous chemotherapy regimens for advanced or MBC.
Population: Number of patients = 511, age range 26 to 79 years, median age = 52 years
Interventions: Patients were randomised to receive either: (1) CAP+ DOC (n = 255): oral capecitabine (CAP) at 1250 mg per m ² twice daily on days 1-14 followed by 7 days rest plus docetaxel (DOC) at 75 mg per m ² i.v. over 1 hour on day 1 every 3 weeks (2) DOC monotherapy (n = 256): DOC at 100 mg per m ² i.v. over 1 hour on day 1 every 3 weeks Dose modifications were applied for all adverse events of grade 2 and above. CAP was reduced to 950 mg per m ² twice per day and DOC to 55 mg per m ² .
Outcomes: Overall survival (OS) (Other outcomes reported include time to progression, overall response rate and safety. QOL was not reported.)
Follow up: -
Results: 670/1317 cycles of CAP + DOC were given with both drugs at full dose 405/1317 cycles of CAP + DOC were given with reduced (950 mg per m ²) CAP and reduced (55 mg per m ²) DOC. These groups were compared for efficacy and safety outcomes. Grade 3/4 adverse events (specifically hand-foot syndrome, stomatitis, diarrhoea or neutropenic fever) occurred in 34% full dose cycles compared with 17% of cycles where both drugs were of reduced dose. Grade 2 adverse events were not significantly different between patients receiving full or partial dose drugs. Median OS in the full dose group (n = 53 patients) was 13.1 months and in the reduced dose group (n = 33 patients) was 16.3 months (NSD).
General comments: This paper presented a retrospective analysis of a large (n = 511) RCT comparing docetaxel and capecitabine vs capecitabine monotherapy for MBC patients previously treated with anthracyclines. Efficacy data were analysed retrospectively with regard to the effect of drug dose reductions. Kaplan Meier survival analysis was used to compare patients who received combined therapy dose reductions by treatment cycle 2 with those who completed at least four cycles without dose reductions.

The patient numbers in this sub-analysis were fairly low compared with the size of the original cohort which weakens the statistical significance. The authors confirm the limitations of this retrospective analysis and caution that it cannot demonstrate superiority even though the median OS results appear to suggest a survival advantage in favour of dose reduction.

These results may be added to the evidence from the original trial report (O'Shaughnessy *et al.*, 2002) which suggested superior efficacy for the CAP + DOC combined therapy over DOC monotherapy.

Miles, D *et al.* (2004)

Design: Randomized controlled trial (prognosis) evidence level: 3

Country: Multi-centre

Inclusion criteria:

Female patients ≥ 18 years with histologically or cytologically confirmed breast cancer with unresectable locally advanced and/or MBC

At least one bidimensionally measurable lesion that had not been irradiated, with a minimum size in at least one diameter ≥ 20 mm (liver) and ≥ 10 mm (lung, skin, lymph node) metastases

Recurrence after anthracycline treatment

Karnofsky performance score $\geq 70\%$

Life expectancy ≥ 3 months

Written informed consent.

Full details of inclusion criteria are given in O'Shaughnessy *et al.* (2002).

Exclusion criteria:

Previous treatment with docetaxel-containing regimen in adjuvant or advanced disease setting

Previous treatment with three or more previous chemotherapy regimens for advanced or MBC.

Full details of exclusion criteria are given in O'Shaughnessy *et al.* (2002).

Population:

Number of patients = 511, age range 26 to 79 years, median age = 52 years

Interventions:

Patients were stratified according to whether or not they had received prior paclitaxel therapy:

(1) CAP + DOC (n = 255): oral capecitabine (CAP) at 1250 mg per m² twice daily for 14 days followed by a 7-day rest period plus docetaxel (DOC) at 75 mg per m² as a 1 hour i.v. infusion on day every 3 weeks

(2) DOC monotherapy (n = 256): DOC at 100 mg per m² administered as a 1 hour i.v. infusion on day 1 every 3 weeks.

Outcomes:

Overall survival (OS)

Follow up:

This report details patients after a follow-up period of ≥ 27 months, an update on the original paper which reported after 15 months.

Tumour responses were evaluated according to WHO criteria at 6 week intervals until week 48 then at 12 week intervals until disease progression.

Results:

After a minimum follow-up period of 27 months:

Median OS for CAP + DOC: 14.5 months (95% CI: 12.3-16.3, 82% of events) vs median OS for DOC = 11.5 months (95% CI: 9.8-12.7, 87% of events). HR = 0.777 (95% CI: 0.645-0.942) P < 0.01

Post-study therapy:

198/256 DOC patients received ≥ 1 post-study treatment. Of these, 28 patients received CAP and 128 patients received other chemotherapy. Patients receiving CAP had median OS = 21 months (95% CI: 15.6-27.6) versus other therapies with median OS = 12.3 months (95% CI: 10.5-14)(HR = 0.5) P = 0.0046

Of the original 255 CAP + DOC patients, 45 had discontinued DOC before progression and continued with single CAP and 34 patients had discontinued CAP before progression and continued with single DOC. Both groups had similar survival: median OS = 18.3 months (95% CI: 14.5-23.4) for CAP versus 15.8 months (95% CI: 9.9-21.5) for DOC (HR = 0.72) P = 0.2

General comments:

Interim data published as Leonard *et al.* (2001) Vukelja *et al.* (2001) Twelves *et al.* (2001) and O' Shaughnessy *et al.* (2002) papers that are included in the capecitabine HTA.

This is a retrospective analysis of post-study therapy.

For the purposes of post-study therapy, prior to disease progression, CAP/DOC patients taken off DOC were considered as remaining on combination study therapy but CAP/DOC patients taken off CAP were considered to be receiving DOC as post-study therapy.

Recruitment: In the original study, patients were recruited at a similar stage in their disease and represented the MBC population as a whole.

Allocation: Post-study treatments were fully detailed in the first instance but there were many discrepancies between reported patient numbers in the 'Introduction' compared to the 'Results' section of this paper which made meaningful interpretation difficult. Personal communication with the lead author revealed that patient drop-out rates had not been reported and hence numbers do not tally between tables, text and graphs.

Maintenance: Clearly, patients were left out of the final analysis but as this is not documented the reasons are not known. Minimum follow-up time was quoted.

Measurement: Post-study treatments were given at the discretion of their clinician. There was no element of blinding etc. This is a retrospective analysis of data.

OS was reported with Kaplan-Meier survival analysis. Median OS was reported with 95% CI and a hazard ratio with log rank P was calculated between the two arms of post-study chemotherapy treatments.

The authors conclude that the results show a clear survival advantage for patients receiving either a CAP/DOC combination therapy or sequential treatment with both agents.

Carrick *et al.* (2005)

Design: Systematic review of RCTs (therapy) evidence level: 1++

Country: Australia

Inclusion criteria:

Included studies:

<p>Properly randomised controlled trials (RCTs) comparing combination chemotherapy with single agent chemotherapy. Trials that included women with both stage III and stage IV breast cancer were required to have reported data separately for these sub-groups. Included patients: Women with advanced (metastatic) breast cancer, either newly diagnosed or with recurrent disease.</p>
<p>Exclusion criteria: None stated.</p>
<p>Population: Number of patients = 7,093</p>
<p>Interventions: Combination chemotherapy regimes versus single agent chemotherapy:</p> <p>1] Regime 1: any drug combination (including drug A) vs drug A alone 2] Regime 2: any drug combination (excluding drug A) vs drug A alone.</p>
<p>Outcomes: Primary outcomes: Overall survival (OS) Time to progression (TTP) Progression-free survival (PFS)</p> <p>Secondary outcomes: Tumour response (response rate RR) Toxicity, Quality of life (QOL) Treatment related deaths (not deaths due to disease progression).</p>
<p>Follow up: N/A</p>
<p>Results: Overall survival data available for 86% of randomised participants n = 6,100. (NB: HR < 1 favours combination regimes): HR = 0.88 (95%CI: 0.83-0.94, P<0.0001) There was no significant heterogeneity across trials (P = 0.17). Results were unchanged when only the sub-group of women receiving first-line therapy (n = 5,099) was analysed: HR = 0.88 (95%CI: 0.83-0.94, P < 0.0001)</p> <p>Sub-group analysis for regime (1) (n = 2,716): HR = 0.91 (95%CI: 0.85-0.98, P = 0.02) with 'slightly significant' heterogeneity (P = 0.22) between trials.</p> <p>Sub-group analysis for regime (2) (n = 1504): HR = 0.83 (95%CI: 0.74-0.92, P = 0.0003) with no evidence of heterogeneity between studies (P = 0.32).</p> <p>Time to progression data available for 56% of randomised participants n = 3,988. (NB: HR<1 favours combination regimes): HR = 0.78 (95%CI: 0.73-0.83, P < 0.00001) with significant heterogeneity (P = 0.0002) across included studies. Results were unchanged when only the sub-group of women receiving first-line therapy (n = 3377) was analysed: HR = 0.78 (95%CI: 0.73-0.83, P < 0.00001) with significant heterogeneity (P = 0.002).</p> <p>Sub-group analysis for regime (1) (n = 2,426): HR = 0.79 (95%CI: 0.73-0.85, P < 0.00001) with no evidence of heterogeneity between studies (P = 0.12).</p> <p>Sub-group analysis for regime (2) (n = 1,183):</p>

HR = 0.77 (95%CI: 0.70-0.85, $P < 0.00001$) with significant between studies heterogeneity ($P = 0.0001$).

Tumour response data available for 87% of randomised participants $n = 6184$. (NB: OR > 1 favours combined therapy regimes):
OR = 1.28 (95%CI: 1.15-1.41, $P < 0.00001$) in assessable patients but with significant between studies heterogeneity ($P < 0.00001$). It was noted that there were some differences between studies in the definition of 'tumour response'.

Sub-group analysis for regime (1) ($n = 3,712$):
OR = 1.34 (95%CI: 1.17-1.53, $P < 0.0001$) with significant heterogeneity between trials ($P < 0.00001$).

Sub-group analysis for regime (2) ($n = 2,472$):
OR = 1.19 (95%CI: 1.00-1.41, $P = 0.04$) with significant heterogeneity across studies ($P \leq 0.00001$). 83% of participants in this sub-group were receiving first-line therapy.

Toxicity:

Leukopenia $n = 5,340$

Alopecia $n = 2,859$

Nausea & vomiting $n = 5,754$ (NB: OR > 1 indicates that the toxicity effects are more prevalent with combination regimes).

OR = 1.45 (95%CI: 1.28-1.65, $P < 0.00001$, Alopecia: OR = 1.55 (95%CI: 1.32-1.81 $P < 0.00001$, Nausea & vomiting OR = 1.65 (95%CI: 1.41-1.93 $P < 0.00001$). There was significant between studies heterogeneity ($P < 0.00001$).

Sub-group analysis for regime (1):
Leukopenia ($n = 3,084$): OR = 1.41 (95%CI: 1.19-1.68 $P = 0.0001$)
Alopecia ($n = 1,518$): OR = 5.49 (95%CI: 4.13-7.39 $P < 0.00001$)
Nausea & vomiting ($n = 3,832$): OR = 1.48 (95%CI: 1.23-1.79 $P < 0.0001$)

Sub-group analysis for regime (2):
Leukopenia ($n = 2,256$): OR = 1.50 (95%CI: 1.25-1.79 $P = 0.0001$)
Alopecia ($n = 1,341$): OR = 0.67 (95%CI: 0.54-0.83 $P = 0.0003$)
Nausea & vomiting ($n = 1,922$): OR = 2.09 (95%CI: 1.57-2.79 $P = 0.00001$)

Note that the incidence of alopecia was significantly less with combined therapy.

Quality of life (QOL) was measured and reported in only nine studies using several scales assessing mainly mood, pain, nausea, vomiting, diarrhoea, hair loss, loss of appetite and social functioning. Of these, four studies reported statistically significant differences between combined and single agent therapy but with mixed findings. One trial *et al.* (Heidemann *et al.*, 2002) found that patients receiving mitoxantrone experienced less hair loss, nausea and vomiting than those on FEC. Joensuu *et al.* (1998) found that patients were less physically distressed after six months of epirubicin therapy, including less nausea than those who received cyclophosphamide, fluorouracil and epirubicin followed by vinblastine. However, Nabholz *et al.* (1999) reported that patients in the docetaxel arm of a trial had less nausea and vomiting but that patients in the other arm (mitomycin plus vinblastine) had poorer social functioning. Finally, Simes *et al.* (1994) found that patients in a combination arm (CMFP vs mitozantrone) reported better QOL for pain, mood and nausea & vomiting over the first three months of the trial but lower QOL with regard to hair loss compared single agent mitozantrone.

Sub-group analysis, group (1) ($n = 3975$):
Overall results :

OS: HR = 0.91 (95%CI: 0.85-0.99 P = 0.03) favours combination regimes. No significant heterogeneity.
TTP: HR = 0.79 (95%CI: 0.73-0.85 P < 0.00001) favours combination regimes. No significant heterogeneity.
RR: OR = 1.36 (95%CI: 1.18-1.55 P = 0.0001) favours combination regimes. No significant heterogeneity.
Toxicity: Nausea & vomiting OR = 1.47 (95%CI: 1.22-1.78 P < 0.0001) leukopenia OR = 1.38 (95%CI: 1.15-1.65 P = 0.0004) and alopecia OR = 19.98 (95%CI: 13.03-30.64 P < 0.0001).
Toxicity effects are more prevalent with combination regimes.

Single anthracycline vs anthracycline-containing combinations:

OS: HR = 0.95 (95%CI : 0.86-1.04 P = 0.25) NSD. No significant heterogeneity.
TTP: HR = 0.84 (95%CI: 0.76-0.92 P = 0.0002) favours combination regimes. No significant heterogeneity.
RR: OR = 1.37 (95%CI: 1.15-1.64 P = 0.0005) favours combination regimes. Significant heterogeneity (P = 0.0001).

Single alkylating agents vs alkylating agent-containing combinations:

OS: HR = 0.91 (95%CI: 0.72-1.15 P = 0.45) favours combination regimes. No significant heterogeneity.
RR: OR = 1.63 (95%CI: 1.04-2.55 P = 0.03) favours single alkylating agent regimes. No significant heterogeneity.

Single anti-metabolite vs anti-metabolite containing regimes:

OS: HR = 0.65 (95%CI: 0.50-0.86 P = 0.003) favours combination regimes. Significant heterogeneity (P = 0.01).
RR: OR = 0.59 (95%CI: 0.37-0.94 P = 0.03) favours single anti-metabolite regimes. Marked heterogeneity (P < 0.00001).

Single taxane vs taxane containing regimes:

OS: HR = 0.91 (95%CI: 0.85-1.085 P = 0.02) NSD. No significant heterogeneity.
RR: OR = 1.69 (95%CI: 1.27-2.25 P = 0.0003) favours combination regimes. No significant heterogeneity.

Sub-group analysis, group (2):

Single anthracycline vs non-anthracycline combination regimes.

OS: HR = 0.86 (95%CI : 0.63-1.18 P = 0.16) NSD. No significant heterogeneity.
RR: OR = 1.72 (95%CI: 1.06-2.81 P = 0.22) favours combination regimes. No significant heterogeneity.

Single taxane vs non-taxane, non-anthracycline-containing combination regimes :

OS: HR = 0.83 (95%CI: 0.73-0.94 P = 0.03) favours single taxane regimes. No significant heterogeneity.
TTP: HR = 0.75 (95%CI: 0.67-0.84 P < 0.0001) favours combination regimes. Significant heterogeneity. (P < 0.0001).
RR: OR = 0.74 (95%CI: 0.58-0.95 P = 0.02) favours single taxane regimes. Marked heterogeneity (P < 0.00001).

Single non-taxane, non-anthracycline vs other combination regimes

RR: OR = 2.04 (95%CI: 1.31-3.19 P = 0.002) favours combination regimes. Significant heterogeneity (P = 0.01).

General comments:

This high quality Cochrane systematic review, with meta-analyses of data from 37 eligible trials, compared the use of first or second line chemotherapy regimes containing a combination of

agents to regimes using a single agent for the treatment of women with metastatic breast cancer.

Only published data were used. Hazard ratios were derived for time-to-event outcomes (i.e. overall survival or time to progression) and the fixed effect model was used for meta-analyses. Odds ratios were used for events with dichotomous outcomes (i.e. tumour response). Trials in which both arms received concurrent hormone therapy were included as were those in which specific treatment was recommended upon treatment failure or disease progression. In the case of crossover trials, data were analysed according to the intention-to-treat principle. It was noted that it had not been possible to determine the quality of randomisation in most included studies due to a lack of information provided by the papers' authors.

The authors concluded that combination regimes showed a significant advantage over single agents in terms of tumour response and time to progression and there was also a modest improvement in overall survival but with significantly worse toxicities. Taxanes appeared to be an exception, however, since when added to a regime they did not appear to confer an advantage compared to use as a single agent.

Significant between-studies heterogeneity in several sub-group analyses and lower sub-group numbers indicate that these results must be viewed with some degree of caution.

References to above mentioned papers in the systematic review:

Heidemann E., Stoeger *et al.* (2002) Is first-line single-agent mitoxantrone in the treatment of high-risk metastatic breast cancer patients as effective as combination chemotherapy? No difference in survival but higher quality of life was found in a multicenter randomized trial. *Ann Oncol* **13(11)**: 1717-1729.

Joensuu H., Holli K., Heikkinen M., Suonio E., Aro AR., Hietanen P and Huovinen R (1998) Combination chemotherapy versus single-agent therapy as first- and second-line treatment in. *J Clin Oncol* **16(12)**: 3720-3730.

Nabholtz JM., Senn HJ., Bezwoda WR., Melnychuk D., Deschenes L., Douma J and Vandenberg (1999) Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with. *J Clin Oncol* **17(5)**: 1413-1424.

Simes RJ., GebSKI V., Coates AS., Forbes J., Harvey V., VanHazel G., Tattersall MHN., Abdi E and Brigham, B (1994) Quality of life (QOL) with single agent mitozantrone (MTZ) or combination chemotherapy (CMFP) for advanced breast cancer: a randomised trial. *Proc Am Soc Clin Oncol* **13**: 73.

Takeda *et al.* (2007)

Design: Systematic review of RCTs (therapy) evidence level: 3

Country: United Kingdom

Inclusion criteria:

Patients with MBC (this was true of ~97% in both study arms) or unresectable locally advanced BC (these patients fell outside the licensed indications for GEM use). The greater majority of patients in both arms had received prior anthracycline therapy.

Exclusion criteria:

None stated

Population:

Number of patients = 529, age range 26 to 83 years, median age = 53 years

Interventions:

Patients were randomised to receive either:

1] GEM + PAC (n = 267): Gemcitabine (GEM) at 1250 mg per m² on days 1 and 8 + paclitaxel (PAC) at 175 mg per m² on day 1 every 3 weeks

2] PAC monotherapy (n = 262): PAC at 175 mg per m² on day every 3 weeks

Outcomes:

Overall survival (OS) quality of life (QOL)

(Other outcomes included response rate, time to progression, and survival at 1 year).

Follow up:

The median follow-up at the time of review publication was 15.6 months.

Treatment was stopped due to disease progression in 38% from the GEM + PAC group and 55% of the PAC monotherapy group. How the data from these patients were handled is not described.

Results:

Median OS:

GEM + PAC = 18.5 months (95%CI: 16.5-21.2)

PAC monotherapy = 15.8 months (95%CI: 14.4-17.4)

No P-value was given.

The 95% CI overlap suggests that there is no statistically significant difference between arms in terms of median OS but with Kaplan Meier analysis, the hazard ratio for OS (0.775 (95%CI: 0.627-9.959 P = 0.018) favours the combined therapy arm. This analysis was performed with only 75% of the required outcomes and hence may change with time. Using Cox regression and adjusting for baseline variation the hazard ratio of 0.74 (95%CI: 0.598-0.915 P = 0.006) also favours GEM + PAC.

QOL:

It was reported in one abstract that the global QOL score (measured by the Rotterdam checklist) was significantly better in the combined therapy group than in the PAC monotherapy group but another abstract reported that the global QOL was not significantly different between these arms whilst not describing by which scale this parameter had been measured. No actual data are available on this outcome.

The levels of analgesia use were also reported differently in two abstracts with one finding a significant reduction for women taking combined therapy and the other finding no significant difference in analgesia reduction between arms.

General comments:

This Health Technology Appraisal (HTA) comprises a systematic review of a single RCT data from which were presented in three reports, all of which were published in abstract form (as of May 2007). The evidential quality is therefore low although the review is very thorough.

The methods of allocation and randomisation are not published in the included abstracts. The blinding was described as 'inadequate'. No intention-to-treat-analysis was undertaken.

This review was published before the final report of the trial and, as such, many analyses are still incomplete. The full text report may be available by the time of an update search for this topic.

References included in this review:

O'Shaughnessy J., Nag S., Calderillo-Ruiz G., Jordaan J., Llombart A., Pluzanska A., et al. (2003) Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for

anthracycline pretreated metastatic breast cancer (MBC): interim results of a global phase III study (abstract 25). *Proc Am Soc Clin Oncol* **22**: 7.

Albain KS., Nag S., Calderillo-Ruiz G., Jordaan JP., Llombart A., Pluzanska A., et al. (2004) Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): first report of overall survival. *J Clin Oncol* **22**: 5S.

Moinpour C., Wu J., Donaldson G., Liepa A., Melemed A., O'Shaughnessy J., et al. (2004) Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first line treatment for anthracycline pre-treated metastatic breast cancer (MBC): quality of life (QoL) and pain palliation results from the global phase III study. *J Clin Oncol* **22**: 32S.

Updated evidence (4.3.2)

Summary

Only one additional paper was identified comparing combined and single agent therapies. A poor quality, low patient number RCT (Pacilio *et al.* 2006) gave patients either epirubicin and docetaxel combined or docetaxel monotherapy as first line treatment for metastatic breast cancer. All the women had received epirubicin in the neoadjuvant or adjuvant setting. There was no difference in outcomes for efficacy or survival but there were significantly more adverse events reported for the combined therapy arm (grade 4 leukopenia, and grade 3 nausea and stomatitis).

Reference

Pacilio C., Morabito A., Nuzzo F., Gravina A., Labonia V., Landi G., Rossi E., De Maio M., D'Aiuto G., Botti G Normanno N., Chiodini P., Gallo C., Perrone F., de Matteis A (2006). Is epirubicin effective in first-line chemotherapy of metastatic breast cancer (MBC) after an epirubicin-containing adjuvant treatment? A single centre phase III trial. *Br J Cancer* **94**: 1233-1236.

Evidence table

Question: Sequential or combination chemotherapy for improved outcomes?
Created by: Karen Francis on 18/07/2008

Pacilio <i>et al.</i> 2006
Design: Randomised controlled trial (therapy) Evidence level: 2- Country: Italy
Inclusion criteria: Women with metastatic breast cancer ≤ 65 years of age No previous chemotherapy for metastatic disease Measurable disease ECOG 0-2 Previous adjuvant treatment with anthracycline permissible (maximum dosages stated) if completed > 12 months before Adequate bone marrow, liver and renal function Written informed consent
Exclusion criteria: Brain metastases Previous taxanes as adjuvant therapy History of serious medical conditions Pregnant or lactating

<p>Population: Number of patients = 51 Age range: 35 to 64 years. Median age = 51 years</p>
<p>Interventions: Arm D (n=25): Docetaxel (DOC) at 100 mg per m² Arm ED (n=26): Epirubicin (EPI) at 75 mg per m² and docetaxel (DOC) at 100 mg per m² Both therapies were given on day 1 of a 21-day cycle for 6 cycles. No dose reductions were allowed but treatment delays were permissible for grade ≥ 2 neutropenia and/or ≥ grade 1 thrombocytopenia.</p>
<p>Outcomes: Tumour response (ORR = CR + PR) complete response (CR) partial response (PR) overall survival (OS) stable disease (SD) progressive disease (PD) time to progression (TTP) adverse events</p>
<p>Follow up: Baseline assessments included physical examination, laboratory studies, ECG, echocardiography with LVEF, brain chest and abdominal CT scans, bone scan and skeletal radiographs if required. Echocardiography and tumour evaluation were undertaken every 3 cycles.</p>
<p>Results: The median number of cycles per patient was 6 (range: 2-6) and 81% and 76% of patients in the ED and D arms respectively received all 6 cycles.</p> <p>ED arm (n=26): CR = 4 PR = 14 ORR = 18/25 (72%) (95%CI: 51-88) SD = 4 PD = 3 NE = 1</p> <p>Median TTP after 22 events = 9 months (95%CI: 7-13) Median OS after 15 events = 18 months (95%CI: 15-na)</p> <p>D arm (n=25): CR = 6 PR = 13 ORR = 19/24 (79%) (95%CI: 58-93) SD = 3 PD = 1 NE = 1</p> <p>Median TTP after 23 events = 11 months (95%CI: 9-15) Median OS after 15 events = 21 months (95%CI: 18-na)</p> <p>There was no significant difference between arms for any outcome.</p> <p>Grade 3/4 adverse events: ED arm (n=26) %: Anaemia = 8/0 Leukopenia = 38/35 Neutropenia = 8/77 Febrile neutropenia = 12/0</p>

Fatigue = 4/0
Diarrhoea = 4/0
Nausea = 4/0
Stomatitis = 12/0
Liver = 4/0
DIC = 4/0
RBC transfusion = 4/0

D arm (n=25) 5:
Leukopenia = 48/4
Neutropenia = 16/60
Febrile neutropenia = 4/4
Diarrhoea = 4/0
Liver = 4/0

The incidences of grade 4 leukopenia, and grade 3 nausea and stomatitis were significantly higher in the ED arm.

General comments:

This paper describes the findings from a small RTC comparing EPI and DOC combined therapy with DOC monotherapy in women previously exposed to EPI in the neoadjuvant or adjuvant setting. Patients were enrolled from May 2000 and October 2003 at a single centre. Recruitment closed after this point due to slow accrual rates. The study was very underpowered since, in the original calculation, 154 patients were required to detect a significant difference between arms. The findings should therefore be viewed with caution.

No significant differences were seen for any efficacy or survival outcomes between arms but some adverse events were significantly higher in the combined therapy arm. The authors concluded that there was no advantage in adding EPI to DOC as first line therapy in women that had been previously exposed but relapsed on EPI. This study is small and statistically underpowered and there are no details of allocation, randomisation or degree of independence in those undertaking the tumour assessment. Blinding appears not to have been employed.

4.4 Vinorelbine as first or subsequent line therapy following anthracycline failure

Short summary

The level of evidence on the use of vinorelbine (VIN) as a monotherapy or in combination with other agents is generally of very poor quality consisting mainly of low patient number, non-comparative phase II trials or small RCTs. As such, the findings from these studies should be interpreted with caution. The majority of patients were believed to have had prior anthracycline therapy.

VIN monotherapy

One small, statistically underpowered RCT (Pajk *et al.* 2008) compared VIN with capecitabine (CAP) in a small number of heavily pre-treated women and reported no significant difference in response or survival outcomes but more adverse events (particularly neutropenia) in the VIN group. Two poor quality phase II studies evaluated VIN for women with metastatic disease (Udom *et al.*, 2000 and Zelek *et al.*, 2001) finding that as second or third line treatment response rates of up to 41%, response duration of 4 months and time to progression of ~2.75 months were reported.

VIN combined therapy

Two poor to moderate quality RCTs tested VIN in combination with 5'-fluorouracil (5'-FU) vs docetaxel (DOC) - Bonnetterre *et al.*, 2002) or gemcitabine (GEM) vs VIN - Martin *et al.*, 2007). VIN + 5'-FU combined resulted in similar treatment outcomes as DOC monotherapy but with a higher incidence of neutropenia. VIN + GEM resulted in superior progression-free survival, but not significantly different overall survival or response duration, compared with VIN alone.

Thirteen poor to moderate quality phase II, non-comparative, studies described VIN combined with: trastuzumab (TRZ) (Burstein *et al.*, 2003, Chan *et al.*, 2006, Jahanzeb *et al.*, 2002, Bartsch *et al.*, 2007, De Maio *et al.*, 2007 and Catania *et al.*, 2007), CAP (Ghosn *et al.*, 2006 and Davis, 2007), DOC (Mayordomo *et al.*, 2004), GEM (Ardavanis *et al.*, 2007 and Colomer *et al.* 2006), 5'-FU (Stuart, 2008), mitozantrone (MTZ) (Onyenadum *et al.* 2007), cisplatin (CIS) followed by DOC (Shamseddine *et al.* 2006) and CAP followed by DOC (Ghosn *et al.* 2008).

For all phase II combination studies, the overall tumour response rates ranged from 33-75%, median overall survival from 13-35.8 months, median response duration from 2.6-17.5 months, median time to progression (reported in two studies) from 6.6-8.6 months and median progression-free survival (reported in two studies) from 9.6-9.9 months. The most commonly reported adverse events attributed to VIN were neutropenia, nausea and vomiting and alopecia.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with advanced breast cancer	Vinorelbine alone or in combination with other agents	Systemic therapy without vinorelbine	<ul style="list-style-type: none"> • Tumour response • Progression-free survival • Overall survival • Symptom relief • QOL • Adverse effects

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

(i) Vinorelbine monotherapy

There were two poor quality, low patient number (n = 60), phase II studies evaluating the use of vinorelbine (VIN) as a second, third line (or higher) salvage therapy for MBC (Udom *et al.*, 2000 and Zelek *et al.*, 2001). At least 80% of patients had received previous anthracycline therapy.

Udom *et al.* (2000) reported a 35% (95%CI: 15-59%) overall response rate (ORR) for all patients but 32% for the anthracycline-treated sub-group. Efficacy and survival data were presented without statistical analyses: median response duration (RD) = 4 months and time to progression (TTP) = 2.75 months. The most commonly reported adverse event was neutropenia which ranged in severity from grade 1-3.

Zelek *et al.*, (2001) presented a study in which VIN was given initially at a weekly dose of 30mg per m² which had to be reduced to 25 mg per m² after the first administration due to severe

adverse events in the first six patients. The ORR = 25% (95%CI: 13-41%) and the median time to treatment failure (TTF) = 6 months (range: 2-18+ months). Nine patients experienced grade 4 neutropenia and three patients had neutropenic fever. Other grade 3/4 events included thrombocytopenia (n = 2), anaemia (n = 4) constipation (n = 3) and peripheral neuropathy (n = 3).

(ii) Vinorelbine combined therapy

There were two poor to moderate quality RCTs testing VIN in combination with another drug as therapy for metastatic breast cancer. Bonnetterre *et al.*, (2002) randomised 176 patients to receive either docetaxel (DOC) or VIN plus 5'-fluorouracil (FUN) on a 21-day cycle. All patients had received prior anthracycline therapy either in the adjuvant or first line setting and were sub-grouped on the basis of being sensitive or resistant/refractory to the drug.

There were no significant differences between the two arms in respect of ORR, overall survival (OS) or time to progression (TTP). Median ORR DOC = 43% (95%CI: 32-53%) versus FUN = 38.9% (95%CI: 29-49%) median overall survival (OS) DOC = 16 months (no CI) versus FUN = 15 months (no CI) median TTP DOC = 6.5 months (95%CI: 5.5-8.4 months) versus FUN = 5.1 months (95%CI: 4.4-6.9 months). This also held true for the anthracycline resistant/refractory groups. One notable difference between arms was in the severity of adverse events - the FUN group lost five patients by the cut-off date, all believed to have died from treatment related events (sepsis, diarrhoea and liver failure). The most common adverse event was neutropenia (82% in DOC arm and 67% in FUN arm) followed by stomatitis (40% in FUN arm) and alopecia (44% in DOC arm).

This paper was not of good quality due to the lack of elaboration on methodology e.g. allocation, blinding, randomisation etc so appears to fail in the elimination of bias.

A second RCT (Martin *et al.*, 2007) compared VIN alone with VIN plus gemcitabine (GEM) combined therapy as first, second or third line treatment for MBC. This was a better quality study in respect of randomisation but, as far as is known, the trial participants and reviewers were not blinded to treatment and some of the authors declared an interest in the company which manufactures one of the drugs being tested (GEM).

It is assumed that, since previous anthracycline and taxane treatment was required for study entry, all patients had been treated thus but this has not been clarified. The tumour response rate between arms was not significantly different (P = 0.093). Median ORR VIN = 26% (95%CI: 18-34%) versus VIN plus GEM = 36% (95%CI: 28-45%).

Log rank testing revealed that VIN plus GEM was significantly better than VIN monotherapy in respect of progression-free survival (P = 0.0028) but not in response duration or overall survival. Median PFS: VIN = 6 months (95%CI: 4.8-7.1 months) versus VIN plus GEM = 4 months (95%CI: 2.9-5.1 months) median OS VIN = 16.4 months (95%CI: 11.6-21.1 months) versus VIN plus GEM = 15.9 months (95%CI: 12.6-19.1 months) median RD VIN = 3.7 months (95%CI: 3.0-4.4 months) versus VIN plus GEM = 4.8 months (95%CI: 3.1-6.6 months).

The most common adverse events were neutropenia (61% in VIN + GEM arm and 44% in VIN arm) and febrile neutropenia (11% in VIN + GEM arm and 6% in VIN arm).

There were six phase II studies of varying quality but all with the shortcoming of having no comparator group. Three studies examined the efficacy and safety of a combined treatment of VIN with trastuzumab (T) (Burstein *et al.*, 2003, Chan *et al.*, 2006 and Jahanzeb *et al.*, 2002) one study reported on VIN plus capecitabine (Ghosn *et al.*, 2006) and one on VIN plus DOC (Mayordomo *et al.*, 2004). The results for VIN plus T are broadly overlapping in terms of tumour response – no other parameter was reported in all three studies.

Generally the quality of the phase II studies was poor: non-independent tumour assessment (Mayordomo *et al.*, 2004, Burstein *et al.*, 2003 and Ghosn *et al.*, 2006) lack of patient demographics (Burstein *et al.*, 2003) poorly reported data (Mayordomo *et al.*, 2004, Ghosn *et al.*, 2006 and Jahanzeb *et al.*, 2002). However, Chan *et al.* (2006) was well conducted and presented with sound statistical methodology, Kaplan-Meier analysis and a reasonable patient number.

The outcomes from all phase II studies are summarised in table 4.4.1 below which shows point estimates with or without 95% confidence intervals.

1st author (study size)	VIN combined with	Med ORR %	Med TTP months	Med TTF months	Med OS months	Med PFS months	Med RD months
Burstein (n = 40)	TRZ	ITT: 75 (57-89) A: 88 (47-99) A+T: 73 (45-92)	NR	NR	NR	NR	22 wks (4-94+)
Chan (n = 69)	TRZ	ITT: 58 (45.5-69.8) A: 61.9 A+T: 54.5	NR	6 (5.3-8.6)	23.7 (18.4-32.6)	9.9 (5.6-12.1)	17.5 (12.1-23)
Jahanzeb (n = 30)	TRZ	ITT: 72 78 (62-90)	72 wks (37-138)	NR	Not reached	NR	NR
Ghosn (n = 40)	CAP	70	NR	NR	30.4	10 (7.6-13.6)	NR
Mayordomo (n = 41)	DOC	56.1 (42-70)	12.4	NR	19.6	NR	12.6

Table 4.4.1 Efficacy data for all studies where this information was given or could be extracted. Abbreviations: A anthracycline, A+T anthracycline plus taxane, ITT intention to treat, NR no reported, n number.

All the studies appraised for this question had a minimum 50% of patients pre-treated with anthracycline, either in the adjuvant or metastatic setting. Overall, the standard and quantity of evidence for either vinorelbine as a monotherapy or combined with another agent was weak.

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Evidence tables

Question: Vinorelbine as first or subsequent line therapy following anthracycline failure
Created by: Karen Francis on 12/03/2007

Bonneterre <i>et al.</i> (2002)
Design: Randomized controlled trial (prognosis), evidence level: 2- Country: France
Inclusion criteria: Women with histologically confirmed MBC Measurable or evaluable disease Pre-treatment with anthracycline (either as first line or adjuvant) > 18 years of age WHO PFS ≤ 2 Adequate haematological, renal and liver function Written informed consent.
Exclusion criteria: Only locally advanced disease Prior treatment with taxanes or vinorelbine > 1 line of prior palliative chemotherapy CNS involvement Osteoblastic bone lesions Severe concomitant conditions.
Population: Number of patients = 176. Age range 28 to 79 years, median age = 55 years.

Interventions:

1] Group 1: Docetaxel (DOC) at 100 mg per m² over a 1hr infusion once every 21 days

2] Group 2: 5'-fluorouracil at 750 mg per m² per day continuous infusion on 5 consecutive days and vinorelbine (VIN)(combined as 'FUN') at 25 mg per m² over a 30 min infusion on days 1 and 5 of every 21-day cycle.

Dose reductions (a maximum of 2 for DOC and 5'-FU and 1 for VIN) were made for grade 3 or 4 non-haematological toxicity, neutropenia or a cycle delay of more than 2 weeks. Patients were withdrawn for unacceptable toxicity, disease progression or on request.

Outcomes:

To compare the safety and efficacy of DOC versus FUN in patients with MBC who had relapsed after anthracycline treatment (adjuvant, neoadjuvant or first line).

Primary: Time to progression (TTP) with Kaplan Meier analysis and comparison between groups with log rank test.

Secondary: Tumour response: complete response (CR), partial response (PR), stable disease (SD), disease progression (PD), not evaluable (NE).

Overall survival (OS) with Kaplan Meier analysis and comparison between groups with log rank test.

Safety: adverse events (AEs)

Follow up:

Baseline evaluation included complete medical history, physical examination, complete blood cell counts, biochemical analysis, urinalysis, ECG, echocardiogram or MUGA (for known heart disease) and tumour assessment by appropriate means.

Before each treatment, physical examination, complete blood cell counts, biochemical analysis and urinalysis were repeated and blood counts were again repeated on day 5 of treatment.

Tumour response was evaluated every three cycles and 28 days after the final treatment.

Median follow-up was 30.3 months (range 10.4 - 45 months). At the cut-off date 15 patients in the DOC arm and 22 patients in the FUN arm had not experienced disease progression.

During the study, three patients in the DOC arm died (2 from disease progression and one possibly related to treatment). In the FUN arm, nine patients died (5 thought to be treatment related and 4 from disease progression or non-treatment related event).

Results:

Median number of DOC doses per patient = 6 (range: 1-12)

Median number of FUN doses per patient = 6 (range: 1-9)

Dose reductions were made in 17% of DOC cycles and 44% of FUN cycles. Treatment delays occurred in 3.9% of DOC cycles and 25% of FUN cycles.

Efficacy (ITT population):

Median TTP DOC arm = 6.5 months (95% CI: 5.5 - 8.4 months)

Median TTP FUN arm = 5.1 months (95% CI: 4.4 - 6.9 months) (P = 0.34).

(anthracycline resistant/refractory patients only):

Median TTP DOC arm = 6.2 months

Median TTP FUN arm = 4.3 months (P = 0.13).

15 DOC patients and 22 FUN patients were censored in the ITT population (7 DOC and 8 FUN patients were resistant/ refractory to anthracycline).

Tumour response (DOC n = 68) (FUN n = 90) n(%):

CR DOC = 6 (7), CR FUN = 4 (4.4)

PR DOC = 31 (36), PR FUN = 31 (34.4)

ORR DOC = 37 (95%CI: 32-53) (43%)

ORR FUN = 35 (95%CI: 29-49)(38.9%) (P = 0.69) nsd

SD DOC = 27 (31.4), SD FUN = 17 (18.9)

PD DOC = 13 (15.1), PD FUN = 20 (22.2)

NE DOC = 9 (10.5), NE FUN = 18 (20.0)

Tumour response in patients anthracycline resistant/refractory (DOC n = 31) (FUN n = 39) n(%):

CR DOC = 1 (6.5), CR FUN = 1 (2.6)

PR DOC = 10 (32.3), PR FUN = 8 (20.5)

ORR DOC = 12 (38.7), ORR FUN = 9 (23.1) (P = 0.25) nsd

SD DOC = 10 (32.3), SD FUN = 4 (10.3)

PD DOC = 6 (19.4), PD FUN = 13 (33.3)

NE DOC = 3 (9.7), NE FUN = 13 (33.3)

Median OS DOC arm = 16 months (35 patients censored)

Median OS FUN arm = 15 months (45 patients censored)

Median OS for both DOC and FUN arms in patients who were anthracycline resistant/refractory was 11.5 months.

Most common grade 3 or 4 adverse events DOC / FUN n(%):

Neutropenia = 65 (82) / 60 (67)

Stomatitis = 4 (5) / 36 (40)

Anaemia = 2 (3) / 7 (8)

Thrombocytopenia = 1 (1) / 9 (10)

Nausea/vomiting = 4 (5) / 5 (6)

Diarrhoea = 6 (7) / 1 (1)

Alopecia = 38 (44) / 7 (8)

Asthenia = 8 (9) / 8(9)

Infection = 2(2) / 6 (7)

Anorexia = 3 (3) / 3 (3)

General comments:

This phase III RCT tested single agent docetaxel against the combination of 5'-fluorouracil and vinorelbine (FUN) in the treatment of first or subsequent line therapy.

Patients were recruited from multiple (n = 22) centres in France between 1995 and 1997 and were randomly assigned, on a one to one basis, to either DOC or FUN therapy, stratified according to treatment centre.

It was intended that 90 patients per arm were recruited in order to have 85% power to detect a 60% (DOC arm) or 40% (FUN arm) difference with a type I error of 0.05.

Patient characteristics were 'well balanced between groups' according to the authors but statistics are not shown in support of this statement. Patients in the FUN arm appear to have received more neoadjuvant/adjuvant (and less palliative) chemotherapy than DOC patients but

the difference may not be significant.

All patients had received prior anthracycline treatment. ~40% were deemed to have been anthracycline-resistant/refractory.

There was no significant difference between treatment arms in respect of the response to treatment, duration or overall survival. However, there was higher mortality associated with the FUN regime observed in the death rate due to sepsis (n = 3), diarrhoea (n = 1) and liver failure (n = 1).

The method of patient assignment to treatment groups was not elaborated and there was no mention of allocation concealment. The different way in which the two treatments were dispensed probably made blinding technically impossible. Tumour assessment by imaging was undertaken by an 'external panel of radiologists' - whether or not these reviewers were blinded to treatment allocation is not addressed. These factors reduce the evidence level of this RCT considerably.

Martin *et al.* (2007)

Design: Randomized controlled trial (prognosis), evidence level: 2-
Country: Spain

Inclusion criteria:

Women with histologically confirmed locally recurrent and MBC
Not amenable to RT or curative surgery
Previous therapy with anthracycline and taxane
Maximum of two previous chemotherapy regimes for MBC
WHO status \leq 2
Adequate bone marrow, liver and renal function (parameters defined)
Life expectancy > 12 weeks
Written consent

Exclusion criteria:

Male
Pregnant or breastfeeding
Previous treatment with gemcitabine, vinorelbine or any other (unapproved) drug within 30 days
Active infection
Serious systemic disorder
Previous grade 3 or 4 neurotoxicity
Second primary cancer (except CIS cervix or skin melanoma)
Clinical evidence of brain metastases
Blastic bone metastases as only site of disease
patient being an investigator, site personnel (or family) or any Eli Lilly employee.

Population:

Number of patients = 252. Age range 28 to 82 years, median age = 58 years.

Interventions:

1] Group 1:

VIN monotherapy (n = 127):

Vinorelbine (VIN) was administered at 30 mg per m² on days 1 and 8 of a 21-day cycle, given i.v. over 6-10min

2] Group 2:

VIN + GEM combined therapy (n = 125):

Vinorelbine (VIN) was administered at 30 mg per m² on days 1 and 8 of a 21-day cycle, given i.v. over 6-10 min. This was followed after 30 min by gemcitabine (GEM) administered at 1200 mg

per m² given i.v. over 30 min.

Treatment was discontinued on disease progression, in the interest of the patient (from the investigator's perspective), at the request of the patient or for unacceptable toxicity.

G-CSF treatment was allowed in the event of febrile neutropenia, prolonged neutropenia or infection.

GEM and VIN dosage modification or withdrawal was allowed in the event of unacceptable haematological or non-haematological toxicity as measured by laboratory criteria or at the discretion of the principle investigator.

Outcomes:

To assess the contribution of GEM to the efficacy of the combined VIN + GEM combined therapy.

Outcomes: progression-free survival (PFS), overall survival (OS), response duration (RD)
Tumour response: complete response (CR), partial response (PR), stable disease (SD), disease progression (PD) or non-evaluable (NE).

Follow up:

Baseline abdominal and thoracic CT scans or radiography, bone scans and blood tests were all performed in the four weeks before study. Blood chemistries and counts were repeated at the beginning of each treatment cycle. Blood counts were also done on day 8 of each cycle.

Medical history, physical examination, performance status and tumour measurements were conducted within one week of the first treatment cycle and on the start day of each cycle thereafter. Tumour measurements were also taken every three cycles and compared with those made at baseline.

At the point of first analysis of PFS, after 205 events, 28 patients in group 2 and 18 patients in group 1 had been censored.

Results:

Efficacy data were available for 251 patients (126 in group 1 and 125 in group 2). Safety data were available from 248 patients (125 in group 1 and 123 in group 2)

Group 1 (VIN):

15% patients received VIN as 1st line therapy, 54% as 2nd line therapy and 31% as 3rd line therapy

Group 2 (VIN + GEM):

21% patients received VIN + GEM as 1st line therapy, 52% as 2nd line therapy and 27% as 3rd line therapy

Median PFS group 1: 4 months (95% CI: 2.9-5.1 months)

Median PFS group 2: 6 months (95% CI: 4.8-7.1 months)

P = 0.0028

Median RD group 1: 3.7 months (95% CI: 3.0-4.4 months)

Median RD group 2: 4.8 months (95% CI: 3.1-6.6 months)

P = 0.1

Median OS group 1: 16.4 months (95% CI: 11.6-21.1 months)

Median OS group 2: 15.9 months (95% CI: 12.6-19.1 months)

P = 0.8

Tumour response group 1 (n):
CR (6) + PR (27) = 33 (median = 26 (95% CI: 18-34))
SD = 32
PD = 58
NE = 3

Tumour response group 2 (n):
CR = (6) + PR (39) = 45 (med = 36 (95% CI: 28-45)) P = 0.093
SD = 35
PD = 40
NE = 5

Safety data:

The commonest grade 3 or 4 toxicity was neutropenia reported in 61% of group 2 patients compared with 44% of group 1 patients (P = 0.0074). Febrile neutropenia occurred in 11% patients in group 2 and 6% in group 1 (P = 0.15).

The overall incidence of grade 3 and 4 non-haematological toxic effects were similar except for alkaline phosphatase (7% in group 2 versus < 1% in group 1 (P = 0.009)) and vomiting (31% in group 2 versus 20% in group 1 (P = 0.048)).

General comments:

This paper reports the final results of a phase III RCT (GEICAM 2000-04) which tests vinorelbine monotherapy against a combination therapy of gemcitabine and vinorelbine. Patients were recruited between January 2001 and March 2005 from 37 centres in 6 countries

Patients were randomised at a central point (GEICAM HQ) by means of a previously computer generated random code and were stratified by centre, number of previous treatment lines (i.e. 0, 1 or 2) and presence of visceral metastases (y or n).

The trial was conducted unblinded for reasons that were not explained. There is a likelihood of bias, therefore, since some of the researchers declared an interest in Eli Lilly, the company which manufactures gemcitabine.

Data were analysed on an intention to treat basis. Statistical analyses were appropriate. PFS was presented as Kaplan Meier survival curve.

Authors stated that 'patients were generally well balanced between groups' - there were some (probably non-significant differences) which were highlighted.

Although data for overall tumour response were not significantly difference between groups 1 and 2, the number of patients with PD as their best response was significantly higher in the combination group (46% versus 32% P = 0.022)

65% of patients in group 2 and 79% in group 1 were given further systemic therapy after this trial and hence the results on OS will have been considerably influenced.

Authors conclude that combination therapy provided superior PFS but acknowledge that the influence on OS cannot be determined and that side effects are more severe with combined therapy.

Although patients were stratified by treatment centre, no discussion of this was identified.

Burstein *et al.* (2003)

<p>Design: Phase II study (prognosis), evidence level: 3 Country: United States</p>
<p>Inclusion criteria: Min age of 18yrs Metastatic breast cancer Written informed consent Her2 overexpression of 2+ or 3+ 0, 1 or 2 previous chemotherapy regimes Bidimensionally measurable disease ECOG status 0-2 Life expectancy > 3months LVEF \geq 50% Neutrophils > 1,500 per μl Platelets > 100,000 per μl Bilirubin < 2mg per dl AST < 2x ULN (extended to < 3x ULN in Sept 1999) Glucose < 200 mg per dl RT, chemotherapy or endocrine therapy concluded 2 weeks before (endocrine therapy changed to 1 week before, from Sept 1999)</p>
<p>Exclusion criteria: Prior vinorelbine Prior trastuzumab Active comorbid disease Pregnant or nursing Prior malignancy, besides breast cancer, unless treated with curative intent Neuropathy >grade 1 (NCI CTC) Concurrent anti-neoplastic therapy</p>
<p>Population: Number of patients = 40. Age range 28 to 70 years, median age = 50 years</p>
<p>Interventions: Intervention: trastuzumab at 4 mg per kg i.v. for 90 min then weekly at 2 mg per kg i.v. for 30 min plus vinorelbine at 25 mg per m^2 i.v. followed by 125 ml saline.</p> <p>Vinorelbine dose was adjusted according to the results of weekly blood counts and monthly LFT.</p> <p>LVEF measurements were taken every 8 weeks and patients with asymptomatic decrease of 15% from baseline, or below normal limits, were taken off the protocol.</p> <p>Patients remained on the study until disease progression, withdrawal of consent or unacceptable toxicity.</p> <p>No comparator.</p>
<p>Outcomes: Primary endpoint: overall response rate (ORR) = complete response (CR) + partial response (PR). Also stable disease (SD) and disease progression (PD).</p>
<p>Follow up: Patients were restaged every 8 weeks.</p> <p>Median time on study for all patients was 27 weeks.</p> <p>27 patients were removed from the study for PD, 4 for withdrawal of patient consent and 4 for lowered LVEF.</p>

Results:

Results were reported on an ITT basis.

8/40 patients had previous treatment with anthracycline, of which 7 had a positive response (88% with 95% CI: 47-99%).

15/40 patients had received anthracycline + taxane therapy, of which 11 had a positive response (73% with 95% CI: 45-92%).

In the entire patient population ORR was 75% (27 PR and 3 CR with 95% CI: 57-89%). 2 patients had SD > 6 months and 8 patients had PD.

Median duration of objective response for all patients was 22 weeks (range: 4-94+ weeks).

4 patients withdrew from the study due to cardiac toxicity - of these, 3 had grade 2 (LVEF declined > 20% from baseline or to below 50%) and 1 patient had grade 1 (LVEF declined between 15% and 20%). Grade 2 cardiac toxicity was only observed in patients with prior cumulative anthracycline exposure of > 240 mg per m² and baseline LVEF of 50% and 59%.

A further 7 patients experienced grade 1 cardiac toxicity but whether or not these women were pre-treated with anthracyclines is not recorded.

General comments:

Patients were recruited between December 1998 and November 1999.

10 patients were allowed on to the trial despite not falling within the definitions of the inclusion or exclusion criteria. The results from these patients were included in the overall analysis as they were believed by the authors not be of significance to the endpoints.

Only 58% patients had received prior treatment with anthracyclines (with or without taxanes) though "patients were not necessarily refractory to such therapies."

The response rate was reported separately for anthracycline treated patients but no other demographics are known for this group compared with the patient population as a whole.

Follow-up was complete and sufficient to record the primary endpoint for all patients.

Tumour assessments are unlikely to have been made independently.

There was no comparator.

Chan A *et al.* (2006)

Design: Phase II study (prognosis), evidence level: 3

Country: Australia

Inclusion criteria:

Women over the age of 18 years

Histologically proven MBC

KPS ≥ 70%

At least one bidimensionally measurable lesion

Life expectancy > 16 weeks

Disease-free interval > 6 months between last adjuvant treatment and relapse

Written informed consent

Normal LVEF measured by ECG or MUGA scan

Adequate haematological, renal and liver parameters (details given)
Exclusion criteria: Previous adjuvant anthracycline with a cumulative dose > 360 mg per m ² (doxorubicin) or > 720 mg per m ² (epirubicin) Local relapse only Prior chemotherapy for MBC Previous treatment with a vinca alkaloid or trastuzumab Peripheral neuropathy > grade 2 Serious medical conditions such as cardiac disease Pregnant or lactating CNS or leptomeningeal metastases History of other malignancy other than CIS cervix or BCC skin.
Population: Number of patients = 69. Age range 30 to 74 years, median age = 53 years
Interventions: Treatment was given over a 4-week period: Trastuzumab (T) was administered at an initial dose of 4 mg per kg i.v. over 90 min on day 1 with post injection observation for 60 min. Subsequent weekly trastuzumab was at 2 mg per kg given over 30 min with 30 min observation (withheld subsequently in the absence of adverse reaction). Vinorelbine (VIN) was administered at 30 mg per m ² i.v. over 6-10 min. The first dose was given 2 hours after trastuzumab. The treatment was planned to be continued for a minimum of 8 weeks (2 cycles) but was discontinued at disease progression, unacceptable toxicity or at the patient's request. Vinorelbine dosage was reduced or delayed for grade 3 or 4 neutropenia and permanently withdrawn for peripheral neuropathy > grade 2 or in the case of three consecutive delays. The dose of trastuzumab was not adjusted but was withheld if LVEF fell below 20% from baseline score or > 10% of absolute units to a value below that of the lower limit of normal for the treatment centre.
Outcomes: Primary: Tumour response: complete response (CR), partial response (PR), stable disease (SD), disease progression (PD), ORR (CR + PR), clinical benefit (CR + PR +SD) Secondary: Progression-free survival (PFS), overall survival (OS), response duration (RD) and time to treatment failure (TTF), time to response. Safety: Adverse events
Follow up: Baseline evaluations were carried out within 28 days of study entry and included medical history, physical examination, haematological measurements, blood chemistries, KPS, Her2 testing, ECG, LVEF, chest X-ray and tumour measurements by relevant scanning modalities. Tumour response was assessed every 8 weeks or until disease progression. Results were confirmed by an independent review panel. Adverse events and medical history were recorded throughout the study.

Two patients were not assessable due to premature discontinuation (sepsis and patient withdrawal). Five other patients were not assessable having failed inclusion criteria.

Median follow-up = 36.2 months

Results:

All patients were included on an ITT analysis efficacy and patients who had received at least one cycle of therapy were included in the safety data. Patients received a median of 18 VIN administrations (range: 1 - 106) and 24 (range: 1 -124) T administrations. VIN was delayed or cancelled in 26.5% of administrations (haematological toxicity) and T in 6.7% (patient or physician choice).

Tumour response n = 62 n(%):

CR = 9 (14.5)

PR = 30 (48.4)

ORR = 39 (62.9)(95%CI: 49.7-74.8)

SD = 12 (19.4)

Clinical benefit = 45 (72.6) (95%CI: 61.5-83.7)

PD = 11 (17.7)

ORR for ITT population = 58% (95%CI: 45.5-69.8)

ORR for patients with previous anthracyclines = 61.9%

ORR for patients with previous anthracyclines/taxanes = 54.5%

Median time to response = 8.4 weeks (range: 7.1-31.3 weeks)

Median RD = 17.5 months (95%CI: 12.1-23.0 months)

Median TTF = 6 months (95%CI: 5.3-8.6 months)

Median PFS = 9.9 months (95%CI: 5.6-12.1 months)

Median OS (all patients) = 23.7 months (95%CI: 18.4-32.6 months).

Grade 3/4 adverse events (% of patients):

Neutropenia = 83.8

Febrile neutropenia = 2.9 (one patient died from sepsis)

Anaemia = 2.9

Asthenia = 8.8

Infection = 5.9

Peripheral neuropathy = 2.9

Diarrhoea = 2.9

Symptomatic LVEF decline = 1.46 (patient died from cardiac failure)

Asymptomatic LVEF decline = 4.4

General comments:

This paper describes a phase II study of vinorelbine and trastuzumab combined therapy for first line treatment of MBC. The study was conducted with patients recruited between 2000 and 2002 at 20 treatment centres from 13 countries (all but one in Europe).

97.1% patients were Her2 +ve, either grade 3+ by IHC (Dako Hercept test) or grade 2+ and FISH +ve (Pathvysion). All tumour samples were processed at a single central laboratory in Germany.

51.1% patients had received prior treatment with an anthracycline based therapy and 28.9% with anthracycline and taxane.

For an uncontrolled study, this was very well conducted and presented with every attempt made to reduce bias by central testing and independent review. The authors suggest that for Her2 +ve patients combining trastuzumab with vinorelbine makes a well tolerated first line regimen.

Ghosn M <i>et al.</i> (2006)
Design: Phase II study (prognosis), evidence level: 3 Country: Lebanon
Inclusion criteria: Women of at least 18 years of age Histologically proven MBC WHO performance status < 2 At least one bi-dimensionally measurable lesion that had not been irradiated Life expectancy > 3 months Adequate bone marrow, liver and renal function (no parameters given) Written informed consent Ability to comply with the study protocol
Exclusion criteria: Local disease only Prior chemotherapy for MBC Prior vinca alkaloid or capecitabine Peripheral neuropathy in > 2 sites Dysphagia or inability to swallow tablets Malabsorption or other GI condition which would prevention drug absorption Serious disease or significantly active infection Pregnancy or lactation CNS or leptomeningeal metastases History of other malignancy except basal cell skin Ca or CIS cervix.
Population: Number of patients = 30. Age range 30 to 77 years, median age = 54 years
Interventions: Vinorelbine at 25 mg per m ² given i.v. over 6-10 minutes on days 1 and 8 of a three-week cycle. Also capecitabine at 825 mg per m ² to be taken orally twice daily for the first 14 days of a three-week cycle. Treatment was planned for a minimum of eight cycles, if the patient responded, or until disease progression but treatment was discontinued with patient refusal or unacceptable toxicity. Dose reductions of capecitabine were instituted for grade 2 or 3 non-haematological toxicity, after 2nd or 3rd incidences of GI toxicity or after grade 2 or 3 hand-foot syndrome. Vinorelbine was interrupted for grade 3 or 4 haematological toxicity and permanently withdrawn in case of grade 2 peripheral neuropathy.
Outcomes: To contribute to knowledge regarding efficacy and tolerability of vinorelbine and capecitabine combined as first line therapy for MBC. Primary objective: overall response rate (ORR), complete response (CR), partial response (PR) and stable disease (SD). Secondary objective: evaluation of safety, overall survival (OS) and progression-free survival (PFS).
Follow up: Baseline assessment were performed on all patients within three weeks of starting treatment including medical history, physical examination, assessment of performance status, pregnancy test (if needed), ECG, chest X-rays, tumour measurement, ultrasound and bone scans.

On day 1 of each treatment cycle, physical condition was evaluated along with performance status, haematological criteria and blood chemistries. On day 8 of each cycle, complete blood counts were determined. Tumour response was assessed every nine weeks until progression or earlier if progression was suspected.

Results:

Efficacy (ITT population) n (%):

CR = 2 (7%)

PR = 19 (63%)

SD = 6 (20%)

ORR (CR + PR + SD \geq 6 months) = 90%

Survival:

Median PFS = 10 months (95% CI: 7.6 - 13.6 months)

Median OS = 30.4 months (no CI)

Safety:

The median number of treatment cycles per patient was 7 (range: 1-13). Capecitabine dose reduction was necessary for 7 patients and vinorelbine in 1 patient.

Grade 3 or 4 events n (%):

Neutropenia = 4 (13%)

Asthenia = 2 (7%)

Nausea or vomiting = 1 (3%)

General comments:

This paper describes a small prospective study of vinorelbine plus capecitabine first line therapy, carried out in three treatment centres in Lebanon. Patients were recruited in 2001 (April to December).

17/30 (57%) patients had been treated with anthracycline as adjuvant therapy.

The authors maintain that this combination therapy shows robust anti-tumour activity with manageable toxicity, particularly since CSF was not employed.

It is not known by whom the tumour assessments were made or if the reviewer was independent.

Jahanzeb *et al.* (2002)

Design: Phase II study (prognosis), evidence level: 3

Country: United States

Inclusion criteria:

Females and males > 18 yrs

Histologically or cytologically confirmed advanced or MBC

Her2 +ve status

Measurable disease

KPS \geq 70%

Signed consent

Life expectancy > 16 weeks

LVEF > 50%

Adequate bone marrow, renal and hepatic function

Exclusion criteria:

Measurable disease only in bone

Previous cytotoxic therapy for MBC

<p>History of MI within 6 months, other malignancy, CNS metastases or peripheral neuropathy (> grade 2) Pregnant or lactating</p>
<p>Population: Number of patients = 40. Age range 30 to 82 years, median age = 51 years</p>
<p>Interventions: Trastuzumab (T) at 4 mg per kg i.v. for 90 min on day 0 then weekly at 2 mg per kg i.v. for 30 min on days 8, 15 and 22. Following T administration, Vinorelbine (VIN) was given at 30 mg per m² diluted and given i.v.</p> <p>VIN dose adjustments, to 20 mg per m², were made for patients experiencing grade 3/4 haematological toxicity, febrile neutropenia (for 7 days) or grade 4 thrombocytopenia.</p> <p>Whilst dose adjustments were made of VIN in response to adverse events, T dose was not modified unless serious toxicity persisted for 4 weeks despite treatment omissions in which case the patient was withdrawn.</p> <p>Treatment was continued until disease progression or unacceptable toxicity.</p>
<p>Outcomes: Primary: overall tumour response (ORR), time to progression (TTP), overall survival (OS), stable disease (SD), disease progression (PD)</p> <p>Adverse events.</p>
<p>Follow up: Anti-tumour activity was assessed every 8 weeks by radiological scan, MRI or CT scan. This was undertaken by investigators at each treatment centre - there was no central review.</p>
<p>Results: Results: Patients had Her2 overexpression of 2+ (17) and 3+ (22) by IHC and 1 patient was FISH +ve.</p> <p>37/40 patients were evaluated for tumour response (the other 3 patients were included for survival analysis).</p> <p>ORR (ITT) = 72% ORR = 78% (95% CI: 62-90%) (4 CR + 25 PR) SD = 4 (11%) PD = 4 (11%)</p> <p>ORR for Her2 2+ patients = 58% ORR for Her2 3+ patients = 82%</p> <p>Median TTP = 72 weeks (95% CI: 37-138 weeks) Median OS = not yet reached.</p> <p>Adverse events: Grade 3 (64 events) and 4 (44 events) neutropenia Grade 3 neuropathy (3 events), constipation (1 event) and infusion reaction (1 event), anaemia (1 event). No patients experienced grade 3 or 4 cardiotoxicity or had T withdrawn.</p>
<p>General comments: This paper describes a multi-centre prospective study in the USA. The purpose was to investigate the efficacy and safety of a weekly regime of trastuzumab with vinorelbine as first line treatment for MBC.</p>

Patients were enrolled between March 1999 and May 2001.

Without a control group, as with all such studies, there is no statistical or evidential value in comparing findings from this observational study with historical data from other work as the authors do.

Mayordomo *et al.* (2004)

Design: Phase II study (prognosis), evidence level: 3

Country: Spain

Inclusion criteria:

Histologically proven breast cancer
Measurable metastatic disease
No prior chemotherapy for MBC
Minimum age of 18 years
ECOG = 0-2
Adequate haematological, liver, kidney and heart function (parameters defined)
Life expectancy > 3 months
ECOG status = 0-2
> 3 months since last treatment
Written informed consent

Exclusion criteria:

Non-measurable disease
Pregnancy or lactation
History of prior malignancy, other than cervical CIS or melanoma
Peripheral neuropathy
Brain metastases
Meningeal carcinomatosis

Population:

Number of patients = 41. Age range 23 to 75 years, median age = 58 years

Interventions:

Docetaxel at 60 mg per m² i.v. over 1 hour followed by vinorelbine at 30 mg per m² infused rapidly on day 1 of a 14-day cycle. The cycle was repeated for up to 12 cycles or until disease progression.

Pre-treatment of dexamethasone, ranitidine, diphenhydramine and granisetron was given but not CSF.

Treatment was deferred in the event of persistent myelosuppression and dose reduction was allowed in cases of neutropenic fever.

Outcomes:

To determine the response and toxicity of bi-weekly docetaxel and vinorelbine.

Median time to progression (TTP), median overall survival (OS) and median duration of response (RD) with Kaplan-Meier analysis. Tumour response: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). Overall response rate (ORR = CR + PR).

Follow up:

Treatment response was evaluated on cycles 6 and 12 and every 12 weeks thereafter. Haematological parameters were tested on day 14 of every cycle.

Median follow-up = 15.1 months or to death.

At the time of publication 2/41 patients remained either alive or disease-free. Follow-up is therefore sufficient for all outcomes.

Results:

Efficacy (ITT population) n (%):

CR = 4 (9.8%)

PR = 19 (46.3%)

ORR = 23 (56.1% 95% CI: 42-70)

SD = 6 (14.6%)

PD = 12 (29.3%)

Survival:

Median RD = 12.6 months

Median TTP = 12.4 months

Median OS = 19.6 months

Safety:

Patients received a median of 8 cycles each with median dose intensity of 85%. Haematological toxicity was responsible for 15 cycles on reduced dosage and 34 cycles that were delayed.

Grade 3/4 events n (%):

Neutropenia = 14 (34.1%)

Leukopenia = 10 (24.4%)

Anaemia = 3 (7%)

Thrombocytopenia = 1 (2.4%)

Febrile neutropenia = 14 (34.1%)

Other = 11 (26.8%)

Three patients withdrew from the study early due to febrile neutropenia but there were no treatment related deaths.

General comments:

This paper describes a prospective phase II study of vinorelbine and taxane given together as first line therapy for MBC in several Spanish treatment centres between 2001 and 2002.

The study has the usual limitations of a non-controlled case series and was only moderately well conducted, with appropriate statistics but a lack of confidence intervals reported on survival data. It was also not stated whether or not tumour response evaluation was carried out by an independent assessor.

Neoadjuvant/adjuvant anthracycline-based treatment had been given in 66% of patients but data are not separately reported for this group.

Authors point out that many of the patients that had taken anthracyclines did so such a long period before enrolment that they might not be considered to have been resistant to the drug. They also suggest that there is no apparent cross reactivity between docetaxel and vinorelbine and that together these drugs might even be partially non cross reactive with anthracycline. The quick recovery of patients from myelotoxicity might allow for a 2-week cycle (as opposed to the more usual 3-week cycle).

The advantage of combined therapy over sequential therapy with the same drugs is not discussed.

Udom *et al.* (2000)

<p>Design: Phase II study (prognosis), evidence level: 3 Country: United Kingdom</p>
<p>Inclusion criteria: Advanced breast cancer 2 or more prior chemotherapeutic regimes including a taxane Written informed consent.</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 20. Age range 23 to 71 years, median age = 47 years</p>
<p>Interventions: Vinorelbine monotherapy at 25 mg per m² was given i.v. over 1 hour every two weeks.</p> <p>Dose reductions were employed in patients at high risk of bone marrow suppression from treatment or from previous chemotherapy or patients with poor performance status or combination of these factors.</p> <p>Treatment was planned to continue for 6 months or until disease progression or unacceptable toxicity.</p>
<p>Outcomes: To evaluate two-week vinorelbine administration in the setting of advanced breast cancer treatment.</p> <p>Median time to progression (TTP), median overall survival (OS) and median duration of response (RD). Tumour response: complete response (CR), partial response (PR), no change (NC), progressive disease (PD). Overall response rate (ORR = CR + PR).</p>
<p>Follow up: Baseline evaluation included measurement of metastatic lesions by clinical examination and imaging techniques. Further comparative evaluations were made before, in the middle and at the end of therapy. It was not stated whether or not tumour response was evaluated by an independent reviewer.</p> <p>At the time of writing, there 5 people were still receiving vinorelbine therapy.</p> <p>Length of follow-up not reported. Number of patients still alive and/or without disease progression was not reported.</p>
<p>Results: Efficacy n (%): PR = 4 (27%) in patients treated on 2-week regime throughout PR = 3 (60%) in patients who were changed over to a 2-weekly regime after starting on weekly therapy NC = 3 (20%) in patients treated on 2-week regime throughout NC = 0 in patients who were changed over to a 2-weekly regime after starting on weekly therapy ORR = 7 (35% 95% CI: 15-59) ORR for 19/21 sub-group pre-treated with anthracycline = 6 (32%) NC for 19/21 sub-group pre-treated with anthracycline = 0</p> <p>Survival: Median RD overall = 4 months, mean = 4.3 months Median RD in patients treated on 2-week regime throughout = 3.3 months, mean = 3.6 months Median TTP = 2.75 months, mean = 3.1 months</p>

<p>Safety: Adverse events (grades 1-4) n: Neutropenia = 7 Febrile neutropenia = 1 Local venous reactions = 6 Thrombocytopenia = 1 Neurotoxicity = 1 Nausea = 1</p> <p>There were no treatment withdrawals due to toxicity.</p>
<p>General comments: This paper describes a poor quality, low patient number, prospective phase II study evaluating 2-weekly vinorelbine as third line, or higher, monotherapy. Patients were recruited from a single UK treatment centre between 1997 and 1998.</p> <p>Nineteen patients (95%) had been previously treated with taxane (docetaxel) and an equal number with anthracycline (epirubicin). Anthracycline resistance was defined as early metastasis after neoadjuvant therapy or as lack of response after first line therapy for advanced disease. The number of prior lines of therapy for advanced disease ranged from 2 - 4 (mean = 2, median = 3).</p> <p>Median OS was not reported. The number of patients experiencing progressive disease was not reported. There was no Kaplan Meier survival analysis. Survival data were given without confidence intervals.</p>

<p>Zelek <i>et al.</i> (2001)</p>
<p>Design: Phase II study (prognosis), evidence level: 3 Country: United States</p>
<p>Inclusion criteria: Women of at least 18 years of age with MBC who had experienced taxane failure Pathologically proven recurrence of breast cancer WHO performance status of < 3 Estimated life expectancy > 3 months Bi-dimensionally measurable disease in a non-irradiated area Informed consent.</p>
<p>Exclusion criteria: Chemotherapy or RT less than 3 weeks prior to study entry Higher than grade 1 peripheral neuropathy Hepatic encephalopathy Uncontrolled CNS metastases Pregnancy</p>
<p>Population: Number of patients = 40. Age range 39 to 69 years, median age = 49 years</p>
<p>Interventions: Vinorelbine at 30 mg per m² was given by central i.v. over 30 min once a week was the planned regime. However, this proved not to be supportable due to complications (see results), at which point the standard dose was reduced to 25 mg per m²</p> <p>CSF support was not allowed except in cases of life-threatening neutropenic fever.</p>

Dose modifications or treatment delays were based on observed toxicity informed by weekly blood counts and monitoring of haematological parameters.

Treatment was planned to continue until disease progression, unacceptable toxicity or at the patient's request.

Outcomes:

To assess the tolerance and efficacy of weekly vinorelbine as salvage therapy in MBC patients after failure with taxanes.

Primary outcome:

Objective response rate and delivered dose intensity and toxicity

Secondary outcome:

Time to treatment failure (TTF), overall survival (OS).

Follow up:

Baseline investigations were carried out before treatment initiation. These included physical examination, performance status assessment, haemogram, hepatic chemistry, serum CA 5-3 measurement and diagnostic imaging as required.

Symptoms and toxicities were noted at every weekly visit to outpatients department and clinical assessments were repeated every 4 weeks. Tumour response was evaluated every 8 weeks and is reported on an ITT basis.

Three patients discontinued treatment after the first injection.

Results:

Severe neutropenia (n = 3), neutropenic fever (n = 1), thrombocytopenia (n = 2), anaemia (n = 1) and neurotoxicity (n = 2) in the first 6 patients recruited caused a dose reduction from 30 to 25 mg per m² for them and for all patients following thereafter.

Efficacy:

CR = 0

PR = 10 (25% 95% CI: 13-41%)

SD = 9

7/10 patients refractory to taxanes had an objective response. 3/16 patients who were not resistant to taxanes had an objective response, with no significant difference between groups.

Survival:

Median TTF = 6 months (range: 4-12 months)

Median overall survival = 6 months (range: 2-18+ months)

Adverse events:

Neutropenia = 9 grade 4

Neutropenic fever = 3

Anaemia = 4 at grade 3 or 4

Thrombocytopenia = 2 at grade 3 or 4

Constipation = 3 at grade 3

Peripheral neuropathy = 2 at grade 3

Sepsis = 1 at grade 3.

General comments:

This paper describes a prospective phase II study of vinorelbine as second or third line (n = 28/40) monotherapy for MBC patients with progressive disease who had previously been treated with both anthracyclines and taxanes. Patients were recruited between 1997 and 1999.

Unusually, CNS metastases, poor liver or kidney function, bone marrow involvement or rapidly progressive visceral disease were not exclusion criteria.

33 (81%) patients had received anthracycline as adjuvant therapy, the majority of which were refractory.

Survival data were presented without confidence intervals. Results for anthracycline patients were not separately reported as the main focus of this study was patients refractory or resistant to taxanes.

Updated evidence (4.4)

Summary

Eight extra papers were identified to update the evidence on the use of vinorelbine (VIN) as a monotherapy or in combination with other agents for the treatment of advanced breast cancer and where the patient has previously been treated with anthracycline or where it was contraindicated. All were phase II trials without comparators and therefore weak in their evidential value; many outcomes of interest were not reported or data were poorly presented.

Three prospective phase II studies (Bartsch *et al.*, 2007, De Maio *et al.*, 2007 and Catania *et al.*, 2007) examined the combination of VIN plus trastuzumab (TRZ) in women who were Her2 +ve. Other phase II studies looked at the use of VIN combined with: capecitabine (CAP) (Davis, 2007), gemcitabine (GEM) (Ardavanis *et al.*, 2007 and Colomer *et al.* 2006), 5'-Fluorouracil (5'-FU) (Stuart, 2008), cisplatin (then docetaxel) (Shamseddine *et al.* 2006) and mitozantrone (Onyenadum *et al.*, 2007).

The outcomes from all phase II studies are summarised in table 4.4.2 below. Data are point estimates with or without 95% confidence intervals (or ranges (rge) where stated).

1st author (study size)	VIN combined with	Med ORR %	Med TTP months	Med TTF months	Med OS months	Med PFS months	Med RD months
Bartsch (n = 30)	(oVIN) + TRZ	68	9.0 (7.6-10.3)	NR	NR	NR	NR
De Maio (n = 50)	TRZ	50 (33.8-66.2)	NR	NR	22.7 (19.5-not reached)	9.6 (7.3-12.3)	12 (5-27) for 1 st line
Catania (n = 39)	(oVIN) + TRZ	43 (27-61)	8.9 (5.1-12.7)	NR	NR	NR	10.9 (7.7-14+)
Ardavanis (n = 31)	GEM	35.5	8.6 (3.2-16) responders	NR	14 (1.4-19)	NR	NR
Davis (n = 22)	CAP	33 (17-55)	5.8 (2.8-6.8)	NR	13.5 (6.9-19.9)	NR	6.9 (4.7-13.1)
Stuart (n=61)	5'-FU	54 (39-68)	NR	15 weeks	35.5 weeks	NR	NR
Shamseddine (n=32)	CIS then DOC	53.1	8 (rge: 1-24)	NR	PA: 20 (rge:2-36) AN: 11.5 (rge:1-31)	NR	12 months (rge:8-24)
Onyenadum (n=51)	MTZ	31 (18.7-46.3)	5.1 (3.51-6.78)	3.18 (1.40-4.96)	12.7 (5.5-19.8)	NR	NR

Ghosn (n=40)	CAP then DOC	62.5%	12.3 (10.1-14.5)	NR	35.8 (rge:2-47)	NR	NR
Colomer (n=52)	GEM	52 (38.2-65.8)	NR	NR	24.6 (17.7-31.5)	6.6. (5.5-7.8)	NR

Table 4.4.2 Efficacy data for all studies where this information was given or could be extracted.
Abbreviations: NR no reported, n number, PA prior anthracycline, AN anthracycline naïve, o oral

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Evidence tables

Question: Vinorelbine as first or subsequent line therapy following anthracycline failure
Created by: Karen Francis on 10/07/2008

Ardavanis <i>et al.</i> (2007)
Design: Phase II study (therapy). Evidence level 3 Country: Greece
Inclusion criteria: Histologically confirmed advanced breast cancer Disease progression after an anthracycline and taxane Age > 18 years ECOG status 0-2 Life expectancy > 3 months Adequate haematological criteria (defined) Adequate liver and renal function (defined) Written informed consent
Exclusion criteria: Secondary malignancy
Population: Number of patients = 31. Age range: 31 to 74 years. Median age = 54 years.
Interventions: [1] Oral vinorelbine (VIN) at 60 mg per m ² [2] Gemcitabine (GEM) i.v. at 1000 mg per m ² Combined therapy was given on days 1 and 15 every two weeks of a 28-day cycle. Dose reductions were permissible based on blood counts and clinical judgement. Treatment was continued after a minimum of three cycles in cases of disease progression. For women with stable disease treatment was continued for a maximum of six cycles.
Outcomes: Tumour response: complete response (CR), partial response (PR), Overall response (OR = CR + PR), stable disease (SD), disease progression (PD), time to progression (TTP), overall survival (OS).
Follow up: Baseline assessments included medically history, physical examination, tumour evaluation, performance status, ECG, complete blood count, serum chemistries, liver and renal function tests. The latter were repeated before each treatment administration. Tumour evaluation was conducted every three cycles. After the study, follow-up was every three months.
Results: Efficacy (n=31): CR = 3 PR = 8 OR = 11 (35.5%) SD = 10

PD = 10

Median TTP = 5.3 months overall (95%CI: 1.1-16)
 Median TTP in responders = 8.6 months (95%CI: 3.2-16)
 Median OS = 14 months (95%CI: 1.4-19)

Grade 3 adverse events:

There was once case of each: leukopenia, neutropenia, thrombocytopenia and nausea and vomiting.

General comments:

This paper briefly describes findings from a small phase II study of combined therapy with oral VIN and i.v. GEM in women with advanced breast cancer who had experienced disease progression after previous anthracycline (100%) and taxane (74%) therapy. Participants were enrolled between June 2004 and January 2006 at a single centre.

The authors report that the combined therapy was well tolerated with only mild toxicity and that the oral formulation of VIN had proved more convenient and safer than intravenous VIN. The conclusion reached was that this combination therapy was an active and safe salvage option in breast cancer patients who had failed anthracycline and taxane therapy.

Bartsch *et al.* (2007)

Design: Phase II study (therapy). Evidence level 3

Country: Austria

Inclusion criteria:

Women with metastatic breast cancer
 At least one measurable lesion
 Her2 +ve (3+ with IHC or FISH +ve)
 KPS ≥ 70%
 Life expectancy > 3 months
 LVEF > 50%
 Adequate (defined) haematological parameters
 Adequate liver and renal function
 Women with controlled brain metastases were acceptable
 Prior adjuvant trastuzumab (TRZ) was acceptable

Exclusion criteria:

Prior palliative TRZ

Population:

Number of patients = 30 age range: 30-83 years. Median age = 59 years

Interventions:

[1] TRZ at a loading dose of 8 mg per kg loading dose and then 6 mg per kg over 90 mins on day 1 every three weeks thereafter.

[2] Oral vinorelbine (VIN) at 60 mg per m² on days 1 and 8 every three weeks.

Outcomes:

Primary outcome: Tumour response: complete response (CR), partial response (PR), Overall response (OR = CR + PR), stable disease (SD), disease progression (PD), response duration (RD), clinical benefit ratio (OR + SD ≥ 24 weeks), time to progression, (TTP)

Follow up:

Baseline tests included blood counts and haematological tests (defined) CT scans of chest and abdomen, mammography, ECG and gynaecological examination. Follow-up blood counts were

performed on days 1, 8 and 15 of each cycle. LVEF was assessed every 6 months. Re-evaluation of tumour status was performed every three months.

30 patients were included in the safety analysis. 28/30 women were available for the analysis of efficacy, one patient having been lost to follow-up and a second having discontinued after the first cycle with grade 4 febrile neutropenia and septic renal failure.

The median time of observation was 20 months (range: 5-27 months).

Results:

Efficacy (n=28):

CR = 5 (both women had non-visceral metastases)

PR = 14

OR = 19 (68%)

SD = 6 (for more than 6 months)

PD = 3

CBR = 89%

Median TTP = 9 months (range: 2-22+) (95%CI: 7.63-10.27 months)

Efficacy for women receiving 1st line treatment (n=17):

CR = 4

PR = 10

OR = 14 (82%)

SD = 3 (for more than 6 months)

PD = 0

CBR = 100%

Median TTP = 10 months (range: 2-22+) (95%CI: 8.04-11.96 months)

Efficacy for women receiving 2nd line treatment (n=6):

CR = 1

PR = 2

OR = 3 (50%)

SD = 2 (for more than 6 months)

PD = 1

CBR = 83%

Median TTP = 6 months (range: 2-13) (95%CI: 1.2-10.8 months)

Efficacy for women beyond 2nd line treatment (n=5):

CR = 0

PR = 2

OR = 2 (40%)

SD = 1 (for more than 6 months)

PD = 2

CBR = 60%

Median TTP = 8 months (range: 2-15+) (95%CI: 0.00-18.74 months)

There was a significant correlation between outcomes and treatment line: 1st line vs other lines: P = 0.032 for TTP and P = 0.011 for CBR.

Grade 3/4 adverse events:

Neutropenia = 5

Nausea and vomiting = 1

<p>Thrombocytopenia = 1 Febrile neutropenia = 2 AST elevation = 1 No grade 3/4 cardiotoxicity (one patient had late LVEF elevation to 50% but had received prior anthracycline).</p> <p>Treatment delays occurred in 9 patients due to neutropenia and a 75% VIN dose reduction as necessary for one patient for severe neutropenia. Multivariate analysis showed no correlation between response and prior taxane exposure in the eleven women in whom this analysis was appropriate.</p>
<p>General comments: This paper presents data from a small phase II study of 30 women treated for metastatic breast cancer at a single centre between February 2004 and September 2005. Participants were given trastuzumab and oral vinorelbine every three weeks.</p> <p>18 women received this treatment as first line, 6 as second line, 4 as third line and 2 as fifth line with a total of 321 cycles given overall.</p> <p>The authors conclude that this combined therapy was a valuable treatment option in advanced breast cancer treatment at this dose and schedule. It was well tolerated and was highly effective and prior taxane exposure did not influence either the response or result in excess neuropathy.</p>

<p>Davis (2007)</p>
<p>Design: Phase II study (therapy). Evidence level 3 Country: Australia</p>
<p>Inclusion criteria: Women with metastatic breast cancer At least one measurable lesion KPS \geq 80% Life expectancy > 3 months LVEF > 50% Adequate (defined) haematological parameters Adequate liver, renal and cardiac function Maximum of one previous chemotherapy for metastatic disease Previous treatment with an anthracycline and taxane or unsuitability to have received them Written informed consent</p>
<p>Exclusion criteria: Severe uncontrolled co-morbidities.</p>
<p>Population: Number of patients = 22</p>
<p>Interventions: [1] Vinorelbine (VIN) at 25 mg per m² i.v. on days 1 and 8 of a 21-day cycle. [2] Oral capecitabine (CAP) at 1000 mg per m² twice a day on days 1 and 14 of a 21-day cycle</p> <p>Anti-emetics were given as appropriate. Patients continued treatment for a maximum of 9 cycles (six cycles for those with stable disease) or until disease progression, unacceptable toxicity or patient withdrawal. Delays of therapy for haematological toxicity (defined) resulted in a dose reduction of VIN or withdrawal if the delay exceeded 2 weeks. In some circumstances when VIN was withdrawn CAP was continued.</p>

Outcomes:

Primary outcome: Tumour response: complete response (CR), partial response (PR), Overall response (OR = CR + PR), stable disease (SD), disease progression (PD), clinical benefit ratio (OR + SD \geq 24 weeks)

Secondary outcomes: time to progression (TTP), response duration (RD) and overall survival (OS).

Follow up:

Baseline tests included physical examination, blood counts and serum chemistry (defined), liver and renal function tests, chest X-rays, abdominal and pelvic CT and bone scan, ECG and other tests as appropriate.

During the study patients monitoring included chest X-ray, CT scans and bone scans every three cycles. During follow-up patients were evaluated every three months including toxicity screening, KPS, disease progression and survival. Response evaluation was undertaken every three cycles and any response was to be confirmed after a further four to six weeks.

21/22 patients were assessable for response since one patient was withdrawn after two cycles due to a central line infection. All patients were assessed for toxicity.

Median follow-up was for 13.5 months.

Results:

Efficacy (n=21):

CR = 2

PR = 5

OR = 33% (95%CI: 17-55)

Median RD = 6.9 months (range: 4.7-13.1)

6/7 responders had received prior anthracyclines in the adjuvant setting and 4/7 had also received taxanes

SD = 5

Median RD = 6.8 months (range: 3.9-10)

Median TTP = 5.8 months (95%CI: 2.8-6.8)

Median OS = 13.5 months (95%CI: 6.9-19.9) (ITT analysis)

Grade 3/4 adverse events:

Neutropenia = 10 (one grade 4)

Febrile neutropenia = 1 (two episodes)

Neuropathy = 1 (causing withdrawal after sixth cycle).

64% of patients required a dose reduction of VIN for neutropenia, and 18% of CAP.

General comments:

This paper describes the results from a very small (n=22) phase II study of combined therapy with VIN and CAP given to women with metastatic breast cancer most of whom had been previously treated with anthracycline and taxane. Slow accrual between May 2003 and October 2005 together with safety and efficacy considerations caused early termination of enrolment. In total 123 cycles of therapy were given (median of 6 cycles, range: 1-9).

36% of patients were Her2 +ve and 41% had positive ER or PR status. The data were not separately considered in these sub-groups.

The authors considered this combination suitable as a standard option for the first line therapy of patients with metastatic breast cancer who had received prior treatment with an anthracycline

and taxane (or for those who could not take these drugs). At the point of publication an oral VIN was not then available which, the authors pointed out, would have provided a more convenient route of administration.

De Maio *et al.* (2007)

Design: Phase II study (therapy). Evidence level 3

Country: Italy

Inclusion criteria:

Women with metastatic breast cancer

Her2 +ve (3+ with IHC or FISH +ve)

Measurable disease (to be included in efficacy analysis but not toxicity assessment)

ECOG \leq 2

LVEF > 50%

Adequate (defined) haematological parameters

Adequate liver and renal function

No more than 1 chemotherapy line for metastatic disease

Exclusion criteria:

Symptomatic brain metastases

History of other cancer (other than non-melanoma skin cancer or CIS cervix)

Previous treatment with trastuzumab (TRZ) or vinorelbine (VIN)

Population:

Number of patients = 50 age range: 31 to 81 years. Median age = 54 years.

Interventions:

[1] TRZ at a loading dose of 8 mg per kg loading dose and then 6 mg per kg over 90 mins on day 1 every three weeks thereafter.

[2] VIN at 30 mg per m² on days 2 and 8 for the first cycle and then on days 1 and 8 every three weeks. TRZ was given before VIN

No dose modification of TRZ was permitted but VIN dose was reduced according to blood and clinical toxicity (i.e. grade 3 or 4 neutropenia). VIN was administered for a maximum of 9 cycles but TRZ was continued until disease progression or unacceptable toxicity. TRZ was withdrawn if LVEF measurements were < 44 or declined > 10 points compared to baseline.

Outcomes:

Primary outcome: Tumour response: complete response (CR), partial response (PR), Overall response (OR = CR + PR), stable disease (SD), disease progression (PD), response duration (RD), clinical benefit ratio (OR + SD \geq 24 weeks), time to progression (TTP), progression-free survival (PFS) and overall survival (OS).

Follow up:

Baseline tests included physical examination, blood counts and haematological tests (defined), chest X-rays, abdominal ultrasound and bone scan, ECG LVEF evaluation and tests appropriate to define the prevalent metastatic sites.

After baseline tests, patients were assessed with blood counts before each cycle and biochemical analyses of urine every week. ECG was performed and LVEF evaluated every three cycles or as required.

One patient had toxic death (acute renal failure with concomitant pamidronate for bone metastases), one patient died during the study from disease progression. Other treatment refusals were due to toxicity (n=8), disease progression (n=10) and patient refusal (n=1). Four

patients died from treatment-related cardiac events and there were three cases of LVEF decline. 40/50 patients were available for efficacy analysis. 10 patients were excluded from this analysis due to not having measurable target lesions.

Results:

Efficacy (n=40):

CR = 7

PR = 13

OR = 20 (50% 95%CI: 33.8-66.2)

SD = 11 (lasting > 6 months in 10)

CBR = 75%

Median RD for women receiving therapy as first line = 12 months (range: 5-27)

Survival at July 1st 2006 (data analysis):

PD = 40

Death = 24

Median PFS = 9.6 months (95%CI: 7.3-12.3)

Median OS = 22.7 months (95%CI: 19.5-NA)

Grade 3/4 adverse events (n=50):

Neutropenia = 46%

Febrile neutropenia = 8%

Allergy = 4%

Anaemia = 4%

Leukopenia = 36%

Grade 5 event:

Liver toxicity = 2% (one woman experienced exacerbation of previous HCV-related hepatitis)

General comments:

This paper details outcomes from a phase II study which was undertaken by a single centre between November 4th 2002 and May 11th 2005 and during which time 50 patients were enrolled and given combined therapy with VIN and TRZ for metastatic breast cancer. Although not stated, the VIN may have been given intravenously since the only mention of oral VIN was in reference to another study.

37/50 patients had received previous anthracyclines and 13/50 had received prior taxanes. None of the women had received prior VIN or TRZ in any setting. 315 cycles of VIN were administered (median: 9 cycles range: 1-9) and 487 cycles of TRZ (median: 9 range: 1-50).

All women were Her2 +ve (3+ by IHC n=94% or FISH +ve) and 60% of women were known to be ER +ve with 38% -ve and the rest unknown.

The authors stated that, of all possible factors influencing response (including pre-treatment), elderly patients (no age defined), those with poor performance status and those with longer interval from breast cancer diagnosis appeared to have had the poorest outcomes. Statistics could not be performed due to very low patient sub-groups. The authors concluded that this combination provided an active therapy with a manageable toxicity profile and could be considered in patients previously treated with anthracyclines and taxanes.

Onyenadum *et al.* (2007)

Design: Phase II study (therapy). Evidence level 3

Country: Greece

<p>Inclusion criteria: Histologically documented breast cancer Measurable disease outside prior RT fields Age \geq 18 years Up to two prior chemotherapy regimes for advanced disease Palliative RT allowed if to the non-indicator lesion Life expectancy $>$ 3 months ECOG status \leq 2 Adequate (described) blood counts and haematological parameters Adequate (described) renal and hepatic function Written informed consent</p>
<p>Exclusion criteria: History of malignancy (other than BCC skin or CIS cervix) Previous chemotherapy with vinorelbine (VIN) or mitozantrone (MTZ) Pregnant or lactating Symptomatic brain metastases</p>
<p>Population: Number of patients = 51 age range: 33.5 to 82 years. Median age = 59 years.</p>
<p>Interventions: 1] VIN at 20 mg per m² i.v. over 30 min on days 1 and 8 of a 21-day cycle 2] MTZ at 10 mg per m² i.v. over 15 min on day 8 of a 21-day cycle Treatment was given for 6 cycles or until disease progression or unacceptable toxicity. Treatment was delayed or dosages reduced for both agents in cases of toxicity (defined). Growth factor support was allowed for severe neutropenia.</p>
<p>Outcomes: Primary outcome: Tumour response: complete response (CR), partial response (PR), Overall response (ORR = CR + PR), stable disease (SD), disease progression (PD), non-evaluable (NE), response duration (RD), clinical benefit ratio (OR + SD \geq 24 weeks), time to progression (TTP), time to treatment failure (TTF) and overall survival (OS). Secondary outcomes: Safety and toxicity</p>
<p>Follow up: Baseline tests included medical history, physical examination, blood counts, biochemical and haematological tests (defined), chest X-rays, abdominal ultrasound and radionuclide bone scan and ECG. Assessment of tumour response was undertaken after the first 3 cycles, at the end of the study and every 3 months thereafter. Median follow-up was 22 months (range: 0.82-37.74). 48 women were included in the efficacy analysis. Three patients were excluded as they had entered the study with stable disease and had been treated with VIN + MTZ as maintenance therapy. 22/48 (46%) women completed the course of treatment. Reasons for discontinuation included disease progression (n=19), non-fatal toxicity (n=3), physician's decision (n=1), patient refusal (n=2) or concurrent illness (n=1).</p>
<p>Results: A total of 290 cycles were delivered (median = 5 cycles range: 1-11). Efficacy (ITT analysis) (n=48): CR = 3 (95%CI: 1.31-17.20) PR = 12 (95%CI: 13.64-39.60)</p>

ORR = 31% (95%CI: 18.66-46.25)
 SD = 11 (95%CI: 12.03-37.31)
 PD = 19 (95%CI: 27.77-54.73)
 NE = 3 (discontinued due to grade 4 myelotoxicity, phlebitis and lumbago)

After median follow-up of 22 months, 40 women had tumour progression and 27 had died.
 Median TTP = 5.1 months (range: 1.02-31.80) (95%CI: 3.51-6.78)
 Median TTF = 3.18 months (range: 1.40-4.96) (95%CI: 1.40-4.96)
 Median OS = 12.7 months (range: 8.2-37.74+) (95%CI: 5.50-19.81)

Grade 3/4 adverse events:

Anaemia = 4
 Leukopenia = 20
 Thrombocytopenia = 24
 Nausea and vomiting = 2
 Alopecia = 2

General comments:

This paper describes a phase II study of combined therapy with VIN and MTZ for women having had not more than two prior chemotherapy regimes for advanced breast cancer. 51 women were enrolled at 9 treatment centres in Greece from October 2001 and May 2004. 85% of women received the protocol as 2nd line therapy.

The authors concluded that this combined therapy at these dosages was an effective treatment with manageable (mostly grade 1 or 2) toxicity which might provided an option in the management of women with metastatic breast cancer.

Pajk *et al.* (2008)

Design: Randomised phase II study (therapy). Evidence level 3

Country: Slovenia

Inclusion criteria:

Women with metastatic breast cancer
 Measurable disease
 Previous treatment with anthracycline and taxane (adjuvant or metastatic setting) unless CI
 Age > 18 years
 KPS ≥ 70%
 Written informed consent

Exclusion criteria:

Significant cardiac disease
 CNS metastases
 Sensitivity to fluoropyrimidines
 Neurotoxicity ≥ grade 2
 Previous treatment with 5'-FU, vinca alkaloids or > 2 chemotherapy lines

Population:

Number of patients = 47. Age range: 31 to 71 years. Median age 50/54 years

Interventions:

[1] Vinorelbine (VIN) at 30 mg per m² i.v. on days 1 and 8 every three weeks
 [2] Oral capecitabine (CAP) at 1250 mg per m² twice a day every 14 days in every three weeks.

In those women with a response or stable disease, chemotherapy was given until disease progression, unacceptable toxicity or patient refusal. Drug modifications were made for particular

(not specified) haematological and other toxicities.

Outcomes:

Primary outcome: Tumour response: complete response (CR), partial response (PR), Overall response (OR = CR + PR), stable disease (SD), disease progression (PD)

Secondary outcomes: response duration (RD), clinical benefit ratio (OR + SD \geq 24 weeks), time to progression, (TTP), safety.

Follow up:

Response evaluation was performed one week before randomisation and then every 6 weeks during chemotherapy until disease progression. All patients were eligible to be included in both the efficacy and toxicity analyses.

14 women (6 in CAP and 8 in VIN arms) could not be assessed for tumour response either because of withdrawal due to toxicity or non-compliance with follow-up – these participants were classified as non-assessable.

Survival was estimated after a median follow-up of 17 months.

Results:

Efficacy CAP arm (n=23):

CR = 1

PR = 1

OR = 2 (8.6%)

SD = 5

CBR = 7 (34%)

PD = 10

Not assessable = 6

Efficacy VIN arm (n=24):

CR = 0

PR = 3

OR = 3 (12.5)

SD = 5

CBR = 8 (33%)

PD = 8

Not assessable = 8

Median RD of CAP responders = 4.4 months (range: 1.4-7.5)

Median RD of VIN responders = 4.2 months (range: 2.6-5.1)

Median PFS for CAP = 2.8 months (95%CI: 1.8-6.3)

Median PFS for VIN = 2.6 months (95%CI: 1.7-4.7)

Median OS for CAP = 9.3 months (7.5-not reached)

Median OS for VIN = 11.0 months (8.1-14.6)

Grade 3/4 adverse events in CAP arm (n=23) %:

Nausea = 4

Vomiting = 4

Hand-foot syndrome = 4

Fatigue = 4

Infection = 4

Neutropenia = 4

Grade 3/4 adverse events in VIN arm (n=24) %:

Constipation = 4

Abdominal pain = 13

<p>Fatigue = 13 Infection = 8 Neutropenia = 46 Febrile neutropenia = 13</p>
<p>General comments: This paper reports the findings from a multi-national study which was designed to compare CAP with VIN as therapy after prior anthracycline and taxane for advanced disease. The planned participant size was 72 and hence, having only enrolled women 47 before accrual closed, this study was very underpowered to detect differences between the two treatment groups and, presumably for this reason, no comparative statistics were reported. Nevertheless, the two groups were randomised (no details given) and were well balanced in most respects. More women in the VIN arm had taxane sensitivity and more women in the CAP arm had visceral disease.</p> <p>The treatment protocol was violated in 42.5% of patients, mainly by not following the specific dose reduction (11 in CAP arm and 6 in VIN arm).</p> <p>The authors concluded that, although this was not a meaningful direct comparison, both agents appeared to have equal efficacy for heavily pre-treated patients with metastatic breast cancer although vinorelbine appeared to have more adverse events (although which are non-overlapping between therapies). Apparently the trial was unable to accrue planned numbers due to patient and physician preference of the (then) recent availability of oral CAP.</p>

<p>Shamseddine <i>et al.</i> (2006)</p>
<p>Design: Phase II study (therapy). Evidence level 3 Country: Lebanon</p>
<p>Inclusion criteria: Age between 18-75 years Histologically confirmed metastatic breast cancer At least one measurable lesion No previous treatment with cytotoxic or hormonal therapy except in adjuvant setting Minimum of 6 months since prior chemotherapy ECOG status 0-2 Life expectancy >3months Adequate (defined) haematological parameters Adequate liver and renal function Written informed consent</p>
<p>Exclusion criteria: Pregnancy or lactating Severe coronary artery disease LVEF <50% or serious ECG abnormality History of congestive heart failure Bone only metastases Other cancers (except CIS cervix or BCC skin)</p>
<p>Population: Number of patients = 35. Age range: 22 to 76 years. Median age 49 years</p>
<p>Interventions: Four cycles of: Vinorelbine (VIN) at 30 mg per m² i.v. over 7-10 min on days 1 and 8 of a 21-day cycle and cisplatin (CIS) at 80 mg per m² i.v. over 1 hour on day 1 of a 21-day cycle</p>

After the 4th treatment cycle responding patients were given docetaxel (DOC) at 75 mg per m² i.v. over 1 hour on day 1 every 21 days for a further 4 cycles.

Treatment was delayed or withheld in cases of neutropenia or thrombocytopenia (blood cell counts described). After 2 cycles, patients with stable disease or a positive response were continued but non-responders were taken off the protocol and offered alternative therapy.

Outcomes:

Primary outcome: Tumour response: complete response (CR), partial response (PR), Overall response (ORR = CR + PR), stable disease (SD), disease progression (PD), response duration (RD), time to progression, (TTP) and median survival.

Secondary outcomes: Safety and toxicity

Follow up:

Baseline tests included physical examination, blood counts and haematological tests (defined), chest X-rays, liver ultrasound, bone scan and CT scans appropriate to the patient's condition.

Tumour response was evaluated every two cycles. Physical examination and laboratory and radiological studies were performed after 2 cycles and at the end of treatment (4 cycles).

Median period of follow-up = 14 months (range: 1-36). 32 patients completed the study and were available for assessment.

Results:

183 cycles were administered (median = 6)

After 2 cycles of VIN + CIS response was seen in 27/32 (84.4%) of patients:

CR = 3

PR = 24

SD = 1 (refused DOC)

PD = 4

27/32 continued the study with DOC and were evaluated after 4 cycles:

CR = 5 (2 of these patients were previously PR)

PR = 12

ORR = 17 (53.1%)

Median RD of PR = 8.5 months (range: 1-18)

SD = 5

Median RD of SD = 12.5 months (range: 6-23)

PD = 5

Median TTP = 8 months (range: 1-24)

Tumour response after a median of 14 months follow-up:

CR = 5

Median RD = 12 months (range: 8-24)

PR = 12

ORR = 17 (53.1%)

SD = 6

PD = 9

ORR of women with visceral metastases (n=23) = 47.8%

Survival at 12 months = 62.5%

Survival at 2 years = 37.5%

Median TTP of women previously treated with anthracyclines = 8 months (range:1-24)
 Median OS of women previously treated with anthracyclines = 20 months (range: 2-36)
 Median TTP of women anthracycline naïve = 5.8 months (range:1-12)
 Median OS of women anthracycline naïve = 11.5 months (range: 1-31)

Grade 3/4 adverse events (n = 183 cycles):

Anaemia = 46

Neutropenia = 26

Thrombocytopenia = 39

Neurotoxicity = 22

Vomiting = 31

General comments:

This paper describes a small, well reported, phase II study of a first line combined therapy for metastatic breast cancer of VIN and CIS followed by DOC for responders. 35 women were enrolled between August 2002 and August 2003 but three died before the trial, or in its early stages, of non-treatment related causes. 72% patients had visceral metastases and the remainder had bone, lymph node or skin involvement. 65.6% of women had received adjuvant anthracycline.

Authors reported that responses were observed in women with both visceral and non-visceral metastases. The addition of DOC to the trial did not add appreciably to toxicity but neither did it improve the overall response rate. Women who had prior exposure to anthracyclines had a higher longer median TTP and OS which led the authors to suggest that the regime could not be recommended for those patients who were anthracycline naïve.

Stuart (2008)

Design: Phase II study (therapy). Evidence level 3

Country: UK

Inclusion criteria:

Histologically confirmed locally advanced or metastatic breast cancer

Measurable or evaluable disease

Previous chemotherapy with an anthracycline or with mitozantrone (MIT)

Normal blood count and laboratory parameters (defined)

Exclusion criteria:

Not defined

Population:

Number of patients = 61. Age range: 27 to 78 years. Median age = 50 years

Interventions:

[1] Vinorelbine at 30 mg per m² i.v. per day

[2] 5'-Fluorouracil (5'-FU) at 200 mg per m² per day

Both drugs were given on days 1 and 8 of a 21-day cycle and treatment was continued until disease progressions, unacceptable toxicity, patient withdrawal or physician's decision.

Outcomes:

Primary outcome: Tumour response: complete response (CR), partial response (PR), Overall response (OR = CR + PR), stable disease (SD), disease progression (PD), response duration (RD), clinical benefit ratio (OR + SD ≥ 12 weeks), time to treatment failure, (TTF).

Follow up:

The treatment response was assessed after every two cycles but not always confirmed after a

further four weeks. Six patients were excluded from the analysis of efficacy through ineligibility (n=2) or not receiving treatment (n=4). Toxicity and response data were collected after eight cycles of chemotherapy regardless of treatment that followed.

Results:

Efficacy (n=61):

CR = 4

PR = 24

Not assessable = 9

OR = 28 (46%) (95%CI: 33-59)

OR excluding non-assessable participants = 54% (95%CI: 39-68)

SD = 8

CBR = 36 (59%) (95%CI: 46-71) NB. stable disease > 12 weeks is included here

Median OS = 35.5 weeks

Median TTF = 15 weeks (or 16 weeks excluding 9 patients who only had one cycle)

Efficacy for those previously treated with taxane (n=24):

OR = 50%

SD = 5

Grade 3/4 adverse events (n=61):

Nausea and vomiting = 12

Oral Mucositis = 8

Hand-foot syndrome = 3

Other skin problems = 1

Diarrhoea = 1

Constipation = 8

Peripheral neuropathy = 1

Alopecia = 2

General comments:

This paper briefly describes the outcomes from a phase II trial of combined therapy of VIN and 5'-FU for patients with advanced breast cancer who had been previously treated with an anthracycline or mitozantrone. Participants were recruited between March 1999 and January 2001.

Patients received a total of 256 cycles of chemotherapy (median = 4 cycles, range: 1-21).

The authors acknowledge that it would be impossible to state that this combined therapy is superior to VIN alone or that 5'-FU infusion is superior to a bolus without a randomised study. This study has some limitations in reporting response data but was more focused on dose and administration issues.

Catania *et al.* (2007)

Design: Phase II study (therapy). Evidence level 3

Country: Italy

Inclusion criteria:

Histologically proven metastatic breast cancer

Her2 over-expression (3+ by IHC or FISH +ve)

Measurable disease

≥ 18 years of age

ECOG ≤ 2

Life expectancy > 16 weeks

<p>Pre-treatment with chemotherapy (including anthracyclines and taxanes) acceptable Refractoriness or resistance to prior trastuzumab therapy acceptable Prior radiotherapy and/or surgery acceptable Acceptable (defined) laboratory parameters LVEF >50% measured by ECG Written informed consent</p>
<p>Exclusion criteria: CNS involvement Pregnant or nursing Pre-existing neuropathy > grade 1 Serious illness (not defined) or medical or psychiatric condition</p>
<p>Population: Number of patients = 39. Age range: 28 to 70 years. Median age = 51 years</p>
<p>Interventions: [1] Trastuzumab (TRZ) at a loading dose of 8 mg per kg loading dose and then 6 mg per kg over 90 mins on day 1 every three weeks thereafter. [2] Oral vinorelbine (VIN) at 55 mg per m² on days 1 and 3 every three weeks. No dose modification of TRZ was permitted but VIN dose was reduced according to blood and clinical toxicity (i.e. grade 3 or 4 neutropenia). Both drugs were administered until disease progression, unacceptable toxicity or patient withdrawal.</p>
<p>Outcomes: Primary outcome: Tumour response: complete response (CR), partial response (PR), Overall response (OR = CR + PR), stable disease (SD), disease progression (PD), response duration (RD), clinical benefit ratio (OR + SD ≥ 24 weeks), time to progression, (TTP).</p>
<p>Follow up: After baseline tests, patients were assessed with blood counts every week and liver and kidney function every three weeks. LVEF was evaluated every three months for the first year and every six months afterwards or as required. Tumour evaluation was undertaken every three cycles. 37/39 patients were assessable for response since two patients were lost to follow-up. Incidences of grade 4 neutropenia (n=1), grade 4 febrile neutropenia (n=2) and grade 2 diarrhoea (n=3) and raised laboratory parameters (n=3) led to dose reductions of VIN.</p>
<p>Results: Efficacy (n=37): CR = 2 (both women had non-visceral metastases) PR = 14 OR = 43% (95%CI: 27-61) SD = 17 PD = 4 CBR = 73% (95%CI: 56-86) Median RD = 10.9 months (range: 2-27+) (95%CI: 7.7-14+ months) Median TTP = 8.9 months (range: 2-27+) (95%CI: 5.1-12.7 months) Efficacy for women with ER +ve and PR +ve tumours (n=20): CR = 2 PR = 6 SD = 11 PD = 1</p>

<p>CBR = 85% (95%CI: 62-97)</p> <p>Median RD = 7.6 months (range: 1-24) Median TTP = 14.3 months (range: 2-27) (95%CI: 7.1-21.5 months)</p> <p>Grade 3/4 adverse events: Neutropenia (n=6) Anaemia (n=1) Febrile neutropenia (n=1) AST elevation (n=1) No grade 3/4 cardiotoxicity (one patient had late LVEF elevation to 50% but had received prior anthracycline).</p>
<p>General comments: This paper presents results from a small phase II study testing oral vinorelbine and trastuzumab combination therapy for women with metastatic breast cancer. Participants were recruited from a single centre from January 2004 to January 2006.</p> <p>92% of women were tested Her2 +ve by IHC and the rest by FISH and 50% had tumours that were ER +ve. 29 women received this treatment as first line, 6 as second line and two as fourth and fifth line. 37 patients received a total of 286 cycles (median number: 7 range: 1-16).</p> <p>The authors concluded that this combined therapy appeared to be safe and active in this group of patients and made note of the low rate of cardiotoxicity, which was acceptable even in those previously treated with anthracyclines. They also observed that the oral VIN was preferred by trial participants as they could receive therapy at home rather than as a hospital in-patient.</p>

Colomer <i>et al.</i> (2006)
<p>Design: Phase II study (therapy). Evidence level: 3 Country: Mexico</p>
<p>Inclusion criteria: Histologically confirmed breast cancer Bidimensionally measurable disease Age ≥ 18 years ECOG status ≤ 2 Adequate haematological and other biochemical criteria (defined) Life expectancy > 3 months Written informed consent</p>
<p>Exclusion criteria: Previous chemotherapy for metastatic disease Adjuvant chemotherapy in the previous 12 months Brain or leptomeningeal disease Peripheral neuropathy Active infection Pregnant or lactating Prior malignancy within the previous 5 years (except BCC skin or CIS cervix) Unstable concomitant disease Use of any investigational drug within 30 days prior to study entry</p>
<p>Population: Number of patients = 52. Age range 34 to 81 years. Median age = 64 years</p>
<p>Interventions: 1] Vinorelbine (VIN) at 30 mg per m² i.v. bolus infusion followed immediately by...</p>

2] Gemcitabine (GEM) at 2500 mg per m² i.v. over 60-90 minutes

Both drugs were given on day 1 of a 14-day cycle for 10 cycles with a scheme of dosage reductions and delays in the event of (documented) toxicity. Both drugs were discontinued if the patient experienced bradycardia, grade 3 myalgia, peripheral neuropathy or any grade 4 haematological toxicity.

Outcomes:

Primary outcome: Tumour response: complete response (CR), partial response (PR), Overall response (ORR = CR + PR), stable disease (SD), disease progression (PD), progression free survival (PFS), overall survival (OS). Toxicity.

Follow up:

Baseline evaluation included complete medical history, blood count, physical examination, serum biochemistry, KPS assessment, CT scan of abdomen and thorax and bone scintigraphy. During the study, follow-up included bi-weekly blood count, serum biochemistry, physical examination and toxicity assessment. Tumour evaluation was undertaken after cycles 4 and 10 and every three months thereafter.

All patients were evaluated for toxicity and 50/52 patients for efficacy.

Results:

A total of 414 cycles of chemotherapy were given with a median of 8 cycles (range: 2-10). Dosage adjustments due to toxicity were required for both VIN (n=21) and GEM (n=15). Dose modifications, delays or discontinuation relating to toxicity occurred in 28% of cycles and in 72% of patients.

Efficacy (n=50):

CR = 2

PR = 24

ORR = 52% (95%CI: 38.2-65.8) (ITT: 50%)

SD = 12

PD = 12

ORR for women where KPS of 0 vs KPS of 1-2: ORR = 66.7% vs 37.9% (P=0.045)

Median PFS = 6.6 months (95%CI: 5.5-7.8)

Median OS = 24.6 months (95%CI: 17.7-31.5)

Survival at 1 year = 73.3%

Survival at 2 years = 52.8%

Consolidation therapies at the end of the study included surgery, endocrine therapy (n=5), high dose chemotherapy with stem cell support (n=1), RT (n=1) and additional chemotherapy (n=1).

Grade 3/4 adverse events %:

Neutrophils (ANC) (34.6% grade 3 and 19.2% grade 4)

Leukocytes (15.4% grade 3 and 15.4% grade 4)

Haemoglobin (4% grade 3)

Platelets (1.9% grade 3)

Vomiting = 1.9

Liver transaminases = 5.8

Constipation = 5.8

General comments:

This paper describes the results from a phase II study of VIN+GEM combination therapy as first line therapy for metastatic disease. Women were enrolled between June 2000 and December 2001. Of the 61.5% of women who had previously received adjuvant chemotherapy, two thirds

had been given anthracyclines. The majority of patients had visceral metastases with a median number of sites of 2 (range: 1-4).

The authors concluded from the results that the combination of VIN + GEM was a useful first line regime to use for women that had received anthracyclines and taxanes in the adjuvant setting.

Ghosn M *et al.* (2008)

Design: Phase II study (prognosis), evidence level: 3

Country: Lebanon

Inclusion criteria:

Women of at least 18 years of age

Histologically proven MBC

WHO performance status < 2

At least one bi-dimensionally measurable lesion that had not been irradiated

Life expectancy > 3 months

Adequate bone marrow, liver and renal function (no parameters given)

Written informed consent

Ability to comply with the study protocol

Exclusion criteria:

Local disease only

Prior chemotherapy for MBC

Prior vinca alkaloid or capecitabine

Peripheral neuropathy in > 2 sites

Dysphagia or inability to swallow tablets

Malabsorption or other GI condition which would prevent drug absorption

Serious disease or significantly active infection

Pregnancy or lactation

CNS or leptomeningeal metastases

Use of the anti-viral agent sorivudine or related analogues

History of other malignancy within 5 years previously, except BCC cancer or CIS cervix.

Population:

Number of patients = 40. Age range 36 to 80 years, median age = 57 years

Interventions:

[1] Vinorelbine (VIN) at 25 mg per m² given i.v. over 6-10 minutes on days 1 and 8 of a three-week cycle.

[2] Capecitabine (CAP) at 825 mg per m² to be taken orally twice daily for the first 14 days of a three-week cycle.

Treatment was planned for four cycles after which responding patients received docetaxel (DOC) at 25 mg per m² each week for 12 weeks. Patients who had progressed by the 2nd cycle of VIN + CAP were moved onto DOC and included in the ITT analysis.

Dose reductions or treatment delays occurred in response to (described) grade 3 or 4 haematological or non-haematological toxicities. For those patients who had disease progression after two cycles of VIN + CAP, the 1st injection of DOC was given at full dosage

Outcomes:

Primary objective: overall response rate (ORR), complete response (CR), partial response (PR) and stable disease (SD), clinical benefit ratio (CBR)

Secondary objective: evaluation of safety, overall survival (OS) and response duration (RD).

Follow up:

Baseline assessment were performed on all patients within three weeks of starting treatment including medical history, physical examination, assessment of performance status, pregnancy test (if needed), ECG, chest X-rays, tumour measurement, ultrasound and bone scans.

On day 1 of each treatment cycle, physical condition was evaluated along with performance status, haematological criteria and blood chemistries. On day 8 of each cycle, complete blood counts were determined. Tumour response was assessed every nine weeks until progression or earlier if progression was suspected.

Results:

Efficacy of VIN + CAP (ITT population) n=40:

CR = 2
PR = 20
ORR = 22 (55%)
SD = 13
CBR = 88%
PD = 5

Efficacy of DOC in those responding or stable with VIN + CAP (ITT population) n=40:

CR = 5
PR = 20
ORR = 25 (62.5%) (95%CI: 45.8-77.27)
SD = 3
PD = 12 (included 6 patients who did not receive DOC due to PD or death)

Efficacy of sequential treatment with VIN + CAP then DOC (ITT population) n=40:

CR = 5
PR = 20
ORR = 25 (62.5%)
SD = 5
CBR = 75%
PD = 9

ORR for patients previously treated with adjuvant anthracyclines = 68%

ORR for patients who were anthracycline naïve = 57.14%

Median TTP = 12.3 months (range: 1.5-48) (95% CI: 10.05-14.54)

Median OS = 35.8 months (range: 2-47)

1yr survival rate = 87.5%

2yr survival rate = 57.5%

3yr survival rate = 35%

Safety:

The median number of treatment cycles per patient was 4 (range: 1-5). CAP dose reduction was necessary for 5 patients and VIN dose reduction in 4 patients. DOC dose reduction was required for one patient.

Grade 3 or 4 events relating to VIN + CAP (n=40):

Anaemia = 1
Thrombocytopenia = 1
Neutropenia = 4
Febrile neutropenia = 3

Grade 3 or 4 events relating to DOC (n=35):

Anaemia = 1

Thrombocytopenia = 2
Neutropenia = 1

General comments:

This paper describes the long term results of a phase II study of VIN + CAP combined followed by DOC as 1st line therapy for advanced breast cancer. The study which was undertaken in 3 treatment centres in Lebanon. Patients were recruited between March 2002 and November 2003.

25/40 (62.5%) patients had been treated with anthracycline as adjuvant therapy. 61.3% of patients had visceral metastases and 75% had non-visceral metastases.

The addition of DOC to the combined regime of VIN + CAP did not significantly affect the overall response rate, even though it increased by 18.5%. The results from this trial encouraged the initiation of another randomised trial comparing VIN + CAP with or without sequential weekly DOC.

4.5 Capecitabine and docetaxel as a combined therapy or capecitabine as a monotherapy

Short summary

The level of evidence on the use of capecitabine (CAP) as a monotherapy or in combination with docetaxel (DOC) is generally of poor quality consisting mainly of low patient number, non-comparative phase II studies with one good phase III RCT. As such, the findings from these studies should be interpreted with caution.

CAP monotherapy

Nine phase II studies (El Helw and Coleman, 2005, Fumoleau *et al.*, 2004, Lee *et al.*, 2004, Pierga *et al.*, 2004, Reichardt *et al.*, 2003, Wist *et al.*, 2004, Sezgin *et al.* 2007, Venturini *et al.* 2007 and Yap *et al.* 2007) and one retrospective case series (Leonard *et al.*, 2002) were identified. The majority of patients are believed to have been treated with anthracycline and taxane.

Across all studies, the overall tumour response rates ranged from 10-42%, median overall survival from 9.4-18.1 months, median response duration from 3.8-15.4 months and median time to progression from 3.5-6.6 months. The most commonly reported adverse event was hand-foot syndrome which at grade 3/4 occurred in up to 21% of patients.

CAP combined therapy

The evidence for combined therapy with CAP and DOC comprised one phase III RCT (Chan, 2005) three phase II studies (Mackey *et al.*, 2002, Silva *et al.* 2008 and Mrozek *et al.* 2006) and a retrospective analysis of post-study data (Miles *et al.*, 2004).

The RCT compared CAP + DOC with gemcitabine and reported no significant difference between study arms in overall response rate, median time to treatment failure or response duration. There were higher levels of hand-foot syndrome and diarrhoea in the CAP and DOC arm. Phase II studies offered poor quality and conflicting evidence on reduced doses of CAP and DOC reporting overall tumour response rates ranged from 44-50%, median overall survival of ~19 months (1 study), median response duration of ~ 9.1 months (1 study) months and median time to progression of ~5.5 months (1 study). A post study analysis of a pivotal RCT (O'Shaughnessy *et al.*, 2002) confirmed a survival advantage with CAP and DOC, either combined or sequentially, when compared with either agent as monotherapy.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with advanced breast cancer	Oral capecitabine alone or in combination with docetaxel	Taxane monotherapy (paclitaxel or docetaxel) Vinorelbine Best supportive care	<ul style="list-style-type: none"> Overall survival Progression-free survival Tumour response Adverse events/toxicity QOL Symptom relief

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary**(i) Capecitabine monotherapy**

No randomised controlled trials of capecitabine (CAP) monotherapy were identified. Six phase II uncontrolled studies, presented as full papers, and one retrospective case series were appraised. Of these, five studies reported that all patients (or the great majority) had been pre-treated with both anthracycline and a taxane.

Five studies (Fumoleau *et al.*, 2004, Lee *et al.*, 2004, Pierga *et al.*, 2004, Reichardt *et al.*, 2003 and Wist *et al.*, 2004) report median overall survival (OS) and median time to progression (TTP) with 95% confidence intervals. As a group, these data are similar at about 4 months for median TTP but dissimilar for median OS. Reichardt *et al.* (2003) reports a median OS of 10.1 months with a very narrow 95%CI: (8.2-11.5). Fumoleau *et al.* (2004) had a similar patient number (n = 126) but here the point estimate of OS was much higher at 15.2 months (95%CI: 13.5-19.6).

Two studies (El-Helw and Coleman, 2005) recruited 57 patients of which only 30% had received prior treatment with both anthracycline and taxane. Although the data analysis was presented for this sub-group, the point estimates (median OS = 10 months, median TTP = 6 months) were without confidence intervals. The other study (Leonard *et al.*, 2002), similarly, gave only point estimates of these parameters (median OS = 7.7 months, median TTP = 4.1 months).

Four studies (Lee *et al.*, 2004, Pierga *et al.*, 2004, Reichardt *et al.*, 2003 and Wist *et al.*, 2004) report the median response duration with 95% confidence intervals which overlap broadly at about 8 months. This parameter was not reported by Fumoleau *et al.* (2004). El-Helw and Coleman (2005) gave a figure of 10 months (no 95%CI). The overall response is very different between Reichardt *et al.* (2003) and Fumoleau *et al.* (2004).

Outcomes are summarised below, in Table 4.5.1 and data are shown as point estimates and 95% confidence intervals, where given.

1st author (study size)	Med ORR %	Med TTP months	Med TTF months	Med OS months	Med PFS months	Med RD months

Fumoleau (n=126)	28 (20-36)	4.9 (4.0-6.4)	NR	15.2 (13.5-19.6)	NR	NR
Lee (n=38)	26 (12-40)	4.6 (2.4-6.8)	NR	18.1 (5.6-30.6)	NR	8.9 (6.5-11.4)
Pierga (n=197) *	15 (11-21)	4.8 (4.1-5)	NR	14.7 (9.6-19.8)	NR	8.9 (6.1-11.7)
Reichardt (n=136)	15 (10-23)	3.5 (2.8-4.1)	NR	10.1 (8.2-11.5)	NR	7.5 (6-9.2)
Wist (n=48)	14 (16-42)	3.6 (2.8-4.3)	NR	9.4 (5.5-13.3)	NR	4.5 (0.8-17.8)
El-Helw & Coleman (n=57) **	29	6	NR	10	6	6
Leonard (n=102) ***	20 (12-20)	4.1	NR	7.7	NR	6.9

Table 4.5.1. Abbreviations: OR overall response, TTP time to progression, OS overall survival, RD response duration, NR not reported. * Some patients were pre-treated with both anthracycline and taxane. 152 patients analysed. ** Only 30% patients pre-treated with anthracycline and taxane – results reported for this sub-group. *** Only 22 patients pre-treated with anthracycline and taxane – results reported for all patients

Overall response (OR) rates were estimated as the sum of complete and partial responses to treatment. Median response duration was given as a point estimate and 95%CI in only four out of seven studies.

The studies generally showed poor methodological quality. Licensing information for CAP indicates monotherapy for patients failing treatment with both an anthracycline and a taxane. Only two studies (Lee *et al.*, 2004 and Wist *et al.*, 2004) recruited patients exclusively that had been pre-treated with both regimes, whilst two studies reported that the majority of patients had received both (Fumoleau *et al.*, 2004: 96% anthracycline and 99% taxane) and (Reichardt *et al.*, 2003: 93% anthracycline and 99% taxane) and the remaining three studies enrolled such patients as part of a wider population.

The lack of a control group in all studies means that the results should be treated with great caution. The resultant lack of blinding which, whilst not crucial for an objective end-point such as death, is important for accurately gauging a more subjective outcome such as tumour response. No paper reported the use of independent assessors and, in many cases, no reference was made to the procedure at all and so the probability of bias is strong.

Comparing data from the TA 62 'Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer' it appears that the recommendations are unlikely to be significantly affected by the addition of these more up-to-date studies. Comparing ranges from TA62 with data from these studies:

Median OS in TA62: 8.1-15.2 months vs 9.4-18.1 months from papers in this summary
 Median TTP in TA62: 2.8-6.2 months vs 3.5-4.9 months from papers in this summary
 Median response duration in TA62: 5.0-8.3 months vs 4.5-8.9 months from papers in this summary
 Overall response rates in TA62: 15-28% vs 14-28% from papers in this summary

Reporting of treatment side-effects was, in most cases, thorough and data are summarised below in Table 4.5.2 showing the five most common grade 3/4 events, expressed as a percentage of

each patient population. Leonard *et al.* (2002) reported that 'at least 20% of study patients had experienced adverse events, mostly mild to moderate', commonly hand-foot syndrome, diarrhoea and nausea. Wist *et al.* (2004) did not differentiate between grade 2/3 events, which were reported as 35% hand-foot syndrome and 23% gastrointestinal toxicity.

Adverse event	Fumoleau	Lee	Pierga	Reichardt	El-Helw & Coleman
Hand-foot syndrome	21%	5%	16%	13%	2%
Nausea	4%	NR	3%	3%	8%
Diarrhoea	10%	3%	7%	8%	4%
Vomiting	3%	NR	2%	4%	2%
Stomatitis	NR	3%	NR	NR	2%

Table 4.5.2. Abbreviation: NR not reported

(ii) Capecitabine combined with docetaxel

The current evidence for combination therapy comprised: one phase III RCT comparing CAP (1,250 mg per m² twice daily for 14 days of a 21-day cycle) plus docetaxel (DOC) (75 mg per m²) given as an iv infusion on day 1 of that 21-day cycle against gemcitabine (1 g per m²) on days 1 and 8 of a 21-day cycle with docetaxel as above on day 1) (Chan, 2005).

One observational study which examined a reduced dose CAP (900 mg per m²) twice daily for 14 days of a 21-day cycle plus a reduced dose DOC (30 mg per m²) given as an iv infusion once per week (Mackey *et al.*, 2002).

One post-hoc analysis of a phase III RCT comparing CAP (1,250mg per m² twice daily for 14 days of a 21-day cycle) plus DOC (75 mg per m²) as an iv infusion on day 1 of that 21-day cycle against DOC (100 mg per m²) given as an iv infusion on day 1 of a 21-day cycle (Miles *et al.*, 2004).

The phase III RCT reported on 305 participants (gender not stated) of which only 76% of the 152 patients in the capecitabine/docetaxel (CD) treatment arm and 69% of the 153 patients in the gemcitabine/docetaxel (GD) comparator arm had received prior treatment with anthracycline. Patient characteristics were not detailed at all in the paper as preliminary results had been presented as an abstract at ASCO in 2005. However, access to this abstract was not possible and hence the information is not recorded in this summary.

There were no significant differences between the treatment and comparator arms in respect of overall response rate, median time to treatment failure or response duration. Overall survival was not reported. Grade 3/4 adverse events were thoroughly recorded, of which the statistically significant parameters were hand-foot syndrome (26% in the CD group against 0% in the GD group) and diarrhoea (17% in the CD group against 7% in the GD group).

The observational study showed that a regime of reduced capecitabine with reduced docetaxel resulted in median OS of 18.7 months (95%CI: 8.6–22.9). However, the patient number was very

low (n = 20) and hence the study was, unfortunately, significantly underpowered. The most commonly reported grade 3 events were: hand-foot syndrome (30%), nail disorder (45%), diarrhoea (20%) and asthenia (30%). No grade 4 adverse events were reported. The low study number and lack of comparator make it impossible to determine whether or not the use of a reduced dose of capecitabine and docetaxel is as effective as the standard dose regime and whether or not the side effects are less severe.

The post-hoc analysis reported results of therapy given to patients that had been enrolled in a multi-centre study (O'Shaughnessy *et al.*, 2001) comparing the combined therapy of capecitabine with docetaxel (CD) against single agent docetaxel (DOC). The original report concluded that CD was of higher efficacy than DOC: median OS: 14.5 months (95%CI: 12.3–16.3) vs 11.5 months (95%CI: 9.8–12.7) hazard ratio of 0.77 (P < 0.01).

In this follow-up paper, Miles *et al.* (2004) reported on the influence of post-study treatment and showed that patients enrolled into the CD arm who had subsequently received single agent CAP had a survival advantage over CD patients receiving any other post-study therapy (median OS: 21 month (95%CI: 15.6–27.6) vs median OS of 12.3 months (95%CI: 10.5–14) a hazard ratio of 0.5 (P < 0.005).

Additionally, the order of sequential therapy did not significantly affect outcome since patients who had been treated with DOC followed by CAP compared with patients who had received CAP then DOC had similar median OS (P = 0.2).

The evidence for capecitabine and docetaxel as a combination therapy remains centred on the RCT of O'Shaughnessy *et al.* (2002) and related papers which suggest an advantage of either combination or sequential therapy with these two agents over single agent docetaxel. In the trial of capecitabine and docetaxel against capecitabine and gemcitabine the survival statistics are not yet available but it appears that side effects may be an issue.

The literature search identified two ongoing trials which are currently recruiting...

NCT00083200. This randomized phase II trial is studying two different doses of capecitabine when given together with docetaxel to compare how well they work in treating women with locally advanced or metastatic breast cancer that has not responded to previous anthracycline-based chemotherapy (such as daunorubicin, doxorubicin, or epirubicin). PharmaNet.

NCT00077857. This study will compare the efficacy and safety of label dose Xeloda to that of a lower dose of Xeloda plus Taxotere in patients with locally advanced or metastatic breast cancer after failure of chemotherapy with an anthracycline. The anticipated time on study treatment is until disease progression and the target sample size is 100-500 individuals. Hoffman La-Roche.

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Evidence tables

Question: Capecitabine and docetaxel as a combined therapy or capecitabine as a monotherapy
Created by: Karen Francis on 03/01/2007

Chan (2005)
Design: Randomized controlled trial (prognosis), evidence level: 2- Country: United Kingdom
Inclusion criteria: Eligible patients (gender preference not stated) between the ages of 18 and 70 years and with histologically or cytologically confirmed locally advanced or MBC. Previous treatment with anthracycline (some patients had also received taxanes as neoadjuvant or adjuvant therapy but were only accepted if therapy had ceased at least 6 months before enrolment). Clinically measurable disease (>2 cm) or from CT scan (≥ 1 cm) in at least one dimension. Karnofsky performance scale (KPS) ≥ 70

<p>Platelet count \geq 100,000 per μl Absolute neutrophil count \geq 1,500 per μl Haemoglobin \geq 9 g/dl Amino alanine transferase (AST) and aspartate amino transferase (AST) $<$2.5 x the upper limit of normal (ULN) Normal bilirubin ('normal' not defined) Alkaline phosphatase (AP) \leq 2.5 x ULN Creatinine \leq 1.25 x ULN Calcium \leq 1.2 x ULN In the case of patients with liver metastases: ALT and AST \leq 3.5 x ULN AP \leq 5 x ULN Bilirubin \leq 1.25 x ULN</p>
<p>Exclusion criteria: Nil</p>
<p>Population: Number of patients = 305, median age = 55 years</p>
<p>Interventions: Patients were stratified according to first- or second-line treatment for MBC, presence or absence of visceral disease, KPS of 0-80% or $>$ 80% and prior taxane treatment.</p> <p>Treatment arm received docetaxel (75 mg per m^2) on day 1 with gemcitabine (1 g per m^2) on days 1 and 8 every 21 days (GD).</p> <p>Comparator arm received docetaxel (75 mg per m^2) on day 1 and oral capecitabine (1250 mg per m^2) twice daily on days 1-14 every 21 days (CD). Therapy continued until disease progression or unacceptable toxicity.</p> <p>Dose modifications: Standard dose modifications were made in response to toxicity. After three such dose reductions, patients were withdrawn from the study. Adverse events were assessed according to the NCIC-CTC version 2.</p>
<p>Outcomes: Primary: Progression-free survival (PFS) Secondary: Toxicity, overall response rate (ORR), time to treatment failure (TTF), partial response (PR), complete response (PR).</p>
<p>Follow up: Median follow-up duration was GD: 88 wks (95%CI: 76-99) and CD: 78 wks (95%CI: 70-87).</p> <p>Before each cycle patients were assessed for neutrophil and platelet counts and all 'non-haematological toxicities'. Radiological tumour assessments were made at baseline and every three cycles throughout the study.</p>
<p>Results: Results: Patient characteristics: Little data were given in respect of patient characteristics. An online 2005 ASCO conference abstract was not available for examination. There is no mention of male patients and the study groups are therefore assumed to be female. The authors state that the two arms were 'well balanced in terms of prognostic factors' age, performance status, stage of disease, metastatic sites and hormone and HER2 receptor status (no further details).</p> <p>105 GD patients (69%) had received prior anthracycline compared with 116 (76%) CD patients.</p>

Patients received a median of 6 doses in each arm.

Efficacy:

Three patients did not participate in this analysis: one patient died before treatment and two withdrew consent.

Median PFS:

GD (n = 153) after 89% events: 35 wks (95%CI: 29-37)

CD (n = 152) after 81% events: 35 wks (95%CI: 31-38).

PFS at 6 months: GD = 91% versus CD = 94%

PFS at 1 year: GD = 31% versus CD = 35%

Tumour response:

CR: GD = 7 (5%) versus CD = 4 (3%)

PR: GD = 42 (27%) versus CD = 44 (29%)

ORR (CR + PR): GD = 32% (95%CI: 24.6-39.4) versus CD = 32% (95%CI: 24.2-39) P = 0.9332

Median TTF:

GD = 19 wks (95%CI: 18-20 wks) versus CD = 18 wks (95%CI: 17-19 wks) P = 0.5056

Median response duration:

GD = 36 wks(95%CI: 30-42 wks) versus CD = 42 wks (95%CI: 33-45 wks) P = 0.3131

Safety:

Grade 3 adverse events n (%) in GD group versus CD group:

Hand and foot syndrome: 0 (0%) vs 39 (26%)*

Diarrhoea = 11 (7%) vs 25 (17%)*

Mucositis = 6 (4%) vs 20 (13%)*

Nausea/vomiting = 13 (9%) vs 8 (5%)

Abdominal pain = 1 (< 1%) vs 5(3%)

Asthenia = 11 (7%) vs 16 (11%)

Alopecia = 12 (8%) vs 11 (7%)

Fatigue = 6 (4%) vs 4 (3%)

Myalgia = 5 (3%) vs 3 (2%)

AST/ALT: 12 (8%) vs 7 (5%)

AP: 5 (3%) vs 3 (2%) * statistically significant

Grade 4 adverse events n (%) in GD group versus CD group:

Diarrhoea = 1 (< 1%) vs 2 (1%)

Mucositis = 0 (0%) vs 6 (4%)

Myalgia = 1 (< 1%) vs 1 (<1%)

Laboratory abnormalities:

Grade 3 events n (%) in GD group (n = 152) versus CD group (n = 150):

Febrile neutropenia: 7 (5%) vs 10 (7%)

Neutropenia: 45 (30%) vs 37 (25%)

Leukopenia = 89 (59%) vs 64 (43%)

Thrombocytopenia = 15 (10%) vs 3 (2%)

Anaemia = 6 (4%) vs 3 (2%)

Grade 4 events n (%) in GD group versus CD group:

Febrile neutropenia = 5 (3%) vs 9 (6%)

Neutropenia = 84 (55%) vs 86 (57%)

Leukopenia = 32 (21%) vs 35 (23%)

Thrombocytopenia = 1 (<1%) vs 2 (1%)

Anaemia = 5 (3%) vs 1 (<1%)

Authors stated that adverse events leading to treatment discontinuation were twice as likely to occur in the CD group as in the GD group (28% compared with 13%).

General comments:

This was a phase III randomised controlled study, undertaken at multiple centres (assumed in Europe) between October 2002 and March 2004. The aim was to evaluate the period of progression free survival with docetaxel in combination with either capecitabine or gemcitabine.

This is a phase III RCT setting docetaxel with capecitabine against docetaxel with gemcitabine.

Recruitment: All patients had MBC and were recruited from multiple centres (assumed in Europe). There are almost no data to describe the patient groups, including age, gender (assumed female), performance status, metastases etc.

Allocation: The treatments are well described. Several prognostic factors were employed in the stratification of the two study arms which were stated to be randomised. However, no details of randomisation methods, concealment, blinding etc were given. Such detail might have been presented in the preliminary abstract (Chan, ASCO 2005) which is not available for consultation.

Kaplan-Meier survival analysis was presented for PFS and TTF.

Maintenance: Patient discontinuation was recorded and the reasons given. Median follow-up period was given and was adequate to cover over 80% events in each study arm. All but 3 patients reached the endpoint for PFS, the primary outcome of interest.

Measurements: It is not documented who performed assessments. Outcomes were objective and so blinding was probably unnecessary. Results for overall survival and quality of life are to be published at a later date.

EI-Helw and Coleman (2005)

Design: Observational study (prognosis), evidence level: 3

Country: United Kingdom

Inclusion criteria:

Female patients with MBC who had failed a number of chemotherapy regimens or hormonal treatment.

3 weeks since previous cytotoxic chemotherapy

Written, informed consent.

Exclusion criteria:

None stated.

Population:

Number of patients = 57, age range 20 to 73 years, mean age = 48 years

Interventions:

Patients received 21-day cycles of oral capecitabine at 1000 mg per m² twice daily for 14 days followed by a 7-day rest period. Treatment was applied until the occurrence of tumour progression or unacceptable toxicity.

Adverse events were graded according to NCI, Canada Common Toxicity Criteria. Hand-foot syndrome was graded 1-3. For patients experiencing grade 2 or higher adverse effects a standard dose modification scheme was applied.

No comparator.
Outcomes: Primary: Overall survival (OS), time to progression (TTP) Secondary: Time to treatment failure (TTF), complete response (CR), partial response (PR), stable disease (SD), objective response rate (RR = CR + PR), progressive disease (PD)
Follow up: Baseline medical history, physical examination, chest and abdominal scans (where indicated) and laboratory tests (haematology and blood chemistry) were performed 2 weeks before treatment initiation. Toxicity assessments were made throughout the study and 28 days after last administration.
Results: Patient characteristics: Median performance status (scale not defined): 2 (range 1-3) Histological grade n (%): Grade 1 = 2 (4%) Grade 2 = 11 (19%) Grade 3 = 36 (63%) Grade N/K = 8 (14%) Oestrogen receptor status n (%): Positive = 25 (44%) Negative = 23 (40%) Unknown: 9 (16%) Menopausal status n (%): Premenopausal = 26 (46%) Postmenopausal = 31 (54%) Number of metastatic sites n (%): 1 = 20 (35%) 2 = 24 (42%) 3 = 5 (9%) 4 = 8 (14%) Sites of metastatic disease n (%): Visceral = 45 (79%) Soft tissue = 44 (77%) Bone = 18 (32%) Adjuvant chemotherapy n (%): Anthracyclines = 14 (25) Cyclophosphamide, methotrexate and fluorouracil = 7 (12%) Treatment of metastatic disease n (%): Anthracyclines = 19 (33%) Taxanes = 6 (11%) Anthracyclines and taxanes = 17 (30%) Other chemotherapy or hormonal treatment = 13 (23%) None = 2 (4%) Number of chemotherapy regimes for MBC n (%): 3 = 6 (11%)

2 = 15 (26%)
1 = 27 (47%)
0 = 9 (16%)

Efficacy n (%):

CR = 1 (2%)
PR = 15 (26%)
RR = 16 (28%)
SD = 13 (23%)
PD = 28 (49%)

Median time to first response: 2 months
Median number of cycles to first response = 3 (range 1-5 cycles)
Median response duration for CR and PR patients = 8.5 months
Response duration for CR (n = 1) = 15 months
Median duration for SD patients = 5 months
Median TTF = 6 months
Median PFS = 6 months

Objective responses:

RR of patients failing anthracyclines (n = 19) = 16%
RR of patients failing taxanes (n = 6) = 33%
RR of patients failing anthracyclines and taxanes (n = 17) = 29%
RR of patients who had not received either anthracyclines or taxanes (n = 15) = 40%

Subjective responses n (%):

Improved = 29 (51%)
Not improved = 28 (49%)

Median OS for all patients = 9 months
Median OS for anthracycline pre-treated patients = 5 months
Median OS for anthracycline/taxane patients = 10 months
Estimated OS at 1 year = 37%
Estimated OS at 2 years = 20%

Safety:

Grade 3/4 adverse events n (%):
Hand-foot syndrome = 1 (2%)
Nausea = 4 (8%)
Diarrhoea = 2 (4%)
Vomiting = 1 (2%)
Stomatitis = 1 (2%)

General comments:

Study undertaken between April 1996 and February 2004. The aim was to determine the efficacy and safety of a reduced (80%) dose (1,000 mg) of capecitabine.

Recruitment: All patients had MBC and were recruited from a single secondary care centre in the UK. There was great variety in the degree of metastatic disease, number of sites, menopausal state, tumour grade etc. which probably made this study group representative of the MBC population as a whole. There were no specific exclusion criteria. The sample size is only moderate.

Only 30% of patients had previously received both anthracycline and taxane treatment. It was noted by the authors that patients having received anthracyclines only were probably older, with organ dysfunction and poor performance status.

Allocation: The treatments are well described. No prognostic factors were identified. The survival curves for PFS and OS were drawn for the entire study population.

As there was no comparator group, allocation concealment was not an issue.

Maintenance: One patient discontinued treatment due to a grade 3 adverse event.

All other patients were followed long enough to quote 1- and 2-year survival probabilities but the mean or median follow-up period per patient was not stated.

65% patients reached the outcome of OS since 20 patients were alive at last follow-up. All patients reached the outcome of PFS at last follow-up.

Measurement: The following outcomes were defined: duration of response, time to progression and time to first response.

It is not clear whether or not the single clinician who administered treatment also performed all assessments. Subjective outcomes were recorded but not included in the final analysis. Objective outcomes such as OS and TTP were assessed and no prognostic factors were identified therefore blinding was probably unnecessary.

Tumour response was assessed according to UICC response criteria and adverse events were recorded 'throughout'. Progression-free survival (TTP) and OS were reported with Kaplan-Meier survival analysis. However, only median values without 95% CIs are given for both primary outcomes, which gave no confidence in the estimate.

Fumoleau *et al.* (2004)

Design: Observational study (prognosis), evidence level: 3

Country: France

Inclusion criteria:

Female outpatients 18-75 years with histologically proven locally advanced or MBC

Previous treatment with two or three chemotherapies including an anthracycline and a taxane

Normal haematological, hepatic, renal, and cardiological parameters

ECOG status of 0-2

Life expectancy of > 3 months

Written informed consent.

Exclusion criteria:

None stated

Population:

Number of patients = 126. Age range 30 to 80 years, median age = 54 years

Interventions:

Patients received 21-day cycles of oral capecitabine 1250 mg per m² twice daily for 14 days followed by a 7-day rest period. Treatment was applied for 15 cycles or until tumour progression.

There was a total of 874 cycles of treatment during the study with a median of 6 cycles (range: 1-15) per patient. Median treatment duration = 4.1 months (range: 0.1-13.0). Median daily dose = 1210 mg per m².

Adverse events were graded from 1-4 according to NCI, Canada Common Toxicity Criteria. Hand-foot syndrome was graded 1-3. QOL was assessed using the EORTC questionnaire. For patients experiencing grade 2 or higher adverse effects a standard dose modification scheme was applied.

No comparator.

Outcomes:

Primary: Time to disease progression (TTP) or death in patients without obvious progression.

Secondary: complete response (CR), partial response (PR), objective response (OR), overall survival (OS), stable disease (SD), progressive disease (PD), quality of life (QOL) and safety

Follow up:

At the conclusion of the study, a minimum follow-up of 15 months had been reached for all patients.

Anti-tumour efficacy was evaluated every 3 treatment cycles based on WHO criteria.

Results:

Patient characteristics:

ECOG performance status (%):

0 = 44%

1 = 49%

2 = 7%

Previous lines of chemotherapy (%):

1 = 3%

2 = 52%

3 = 34%

≥ 4 = 11%

Previous chemo agents (%):

Anthracycline = 96%

Taxane = 99%

5-FU = 90%

Sites of metastasis (%):

Bone = 56%

Liver = 55%

Lung = 26%

Lymph node = 23%. 67% patients had multiple metastases. Data unavailable for 1 patient.

Efficacy n (%):

CR = 5 4%

PR = 30 24%

OR = 35 28% (95%CI: 20-36%).

SD = 44 35%

PD = 47 37%

Median TTP = 4.9 months (95%CI: 4.0-6.4)

Median OS = 15.2 months (95%CI: 13.5-19.6)

Estimated survival at 1 year = 62.3%.

Safety:

47 patients required dose reduction due to adverse effects:

Hand-foot syndrome = 17.5%

Neutropenia = 8%

Diarrhoea = 5.5%.
Median time to dose reduction = 1.8 months (95%CI: 1.3-2.5).

Total grade 3/4 adverse events (%):

Hand-foot syndrome = 21%

Diarrhoea = 10%

Neutropenia = 14%

Nausea = 4%

Vomiting = 3%. There were no treatment related deaths.

Laboratory abnormalities:

Grade 3 events (%):

Lymphocytopenia = 48%

Neutropenia = 5%

Anaemia = 1%

Hyperbilirubinaemia = 13%

Phosphatase elevation = 8%

AST elevation = 4%

ALT elevation = 2%.

Grade 4 events (%):

Lymphocytopenia = 10%

Neutropenia = 1%

Thrombocytopenia = 2%

Anaemia = 2%

Hyperbilirubinaemia = 2%

Quality of life:

119/126 patients completed the QOL questionnaire before treatment. At cycle 3, 78% were completed and, at cycle 6, 46%. The authors state: 'mean global health status increased up to cycle 6 with the increase maintained at subsequent evaluations'. The data were not extractable.

General comments:

Study undertaken between Dec 1998 and Oct 2001. Interim data published as Fumoleau *et al* (2001) and (2002). These papers were assessed for the capecitabine HTA.

Recruitment: All patients had MBC and were recruited from are assumed to be secondary care facilities in France. There was great variety in the degree of metastatic disease, number of sites, previous chemotherapy regime etc. which probably made this study group representative of the MBC population as a whole. There were no specific exclusion criteria.

The sample size was reasonable - the authors had, from the median and standard error data from a previous study, determined the likely number of study participants needed to infer a 95%CI.

Allocation: The treatments are well described. No prognostic factors were identified. The survival curves for TTP and OS were drawn for the entire study population.

As there was no comparator group, allocation concealment was not an issue.

Maintenance: A minimum follow-up period of 15 months was reached in all patients.

At the time of writing, the authors stated that 81 patients had died (therefore 36% patients alive). No details were given of the disease progression in the remaining patients and, therefore, the endpoint of this primary outcome was not reached in 64% of the study population.

Authors stated 'patients withdrawing from the trial or lost to follow-up were censored at the date of drop-out or last review'. No further information was given.

Measurements: The following outcomes were defined: time to disease progression and duration of response.

Tumour response was assessed every three cycles, using standard WHO criteria. No details were given of the operator. Objective outcomes such as OS and TTP were assessed and no prognostic factors were identified therefore blinding was probably unnecessary.

In the QOL study, 73/112 patients that had answered the first evaluation did not answer the third, after six cycles. These patients may have given adverse or negative responses. However, this time point is reported to show a significant, positive increase over baseline.

TTP and OS were reported with Kaplan-Meier survival analysis. Median values with 95%CI:s are given for both primary outcomes. The relatively intervals reflect the moderate to high sample size in this study.

Lee *et al.* (2004)

Design: Observational study (prognosis), evidence level: 3
Country: Korea (South)

Inclusion criteria:

Females > 18 years with histologically confirmed MBC

At least one measurable lesion > 2 cm

ECOG status 0-2

Life expectancy of ≥ 3 months

Previous treatment with anthracycline and taxane containing regimen

Absolute neutrophil count (ANC) ≥ 1500 per μl

Platelet count $\geq 100,000$ per μl

Aspartate aminotransferase and alanine aminotransferase ≤ 3 times the upper limit of normal (ULN)

Bilirubin $\leq 1.25 \times \text{ULN}$

Serum creatinine $\leq 1.5 \times \text{ULN}$.

Exclusion criteria:

Patients with previous adverse reaction to 5-FU

Prior history of another malignancy within 5 years of study entry, apart from basal cell carcinoma of the skin or carcinoma in situ of the cervix

Clinically significant cardiac disease (symptomatic ventricular arrhythmias, history of congestive heart failure, previous MI).

Population:

Number of patients = 38. Age range 31 to 66 years, median age = 48 years

Interventions:

Patients received 21-day cycles of oral capecitabine 1250 mg per m^2 twice daily for 14 days followed by a 7-day rest period. Treatment was applied until evidence of progression, unacceptable toxicity, at the request of the patient or at the discretion of the clinician. Patients received a median of 6 cycles (range 1-15 cycles).

Dose modifications:

Drug dosage was adjusted at any time during the study on the basis of adverse events defined by NCIC-CTC version 2.

Chemotherapy was withheld if ANC was <1,000 per µl or platelet count was < 75,000 per µl on day 1. Blood tests were repeated weekly and chemotherapy was resumed when ANC > 1,000 per µl and platelets > 75,000 per µl.

With grade 1 (platelets) or 2 (neutrophils) toxicity the starting dose of capecitabine was reduced by 25%. Development of grade 2 toxicity resulted in temporary interruption of treatment, until toxicity returned to grade 0 or 1, before therapy was resumed at the same dose. With the first grade 3, or second grade 2 toxicity, treatment was interrupted and resumed when toxicity had reached grade 0 or 1 but at 25% dose reduction. If grade 3 toxicity recurred, then dosage was reduced by 50%, and, after a further recurrence of grade 3, or appearance of grade 4, toxicity, dose was reduced by 75%.

At a third recurrence of grade 3 or second recurrence of grade 4 toxicity, treatment was discontinued and the patient was withdrawn from the study.

Outcomes:

Primary: Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), tumour control rate (TCR), objective response rate (OR), sub-group analysis of prognostic factors for TTP and OS.

Secondary: Response duration, time to progression (TTP), overall survival (OS)

Follow up:

Complete medical history, physical examination, blood count, chemistry and X-rays (if relevant) were performed on day 1 of every treatment cycle. CT scans were used to evaluate treatment response every 3 cycles. Compliance was monitored by questioning patients and counting remaining pills at outpatient visits.

Median follow-up period = 27.8 months (range: 7.1-46.7 months).

Results:

Patient characteristics:

ECOG performance status (%):

0-1 = 55%

2 = 45%

Predominant site of metastases (%):

Visceral = 58%

Soft tissue = 34%

Bone = 38%

Number of involved organs (%):

1-3 = 82%

4-5 = 18% Mean number of organs = 2.5

Disease-free survival (%):

0-1 months = 11%

1-12 months = 13%

>12 months = 76%

Mean number of prior systemic therapies:

Chemotherapeutic regimens = 2.9 (range 2-5)

Chemotherapeutic agents = 6.1 (range 3-9)

Taxanes = 1.5 (range 1-2)

Hormonal therapies = (0.5 range 1-3). N.B. last value as reported by authors.

Efficacy (measured in ITT population):

2 patients (5%) withdrew after the start of the study - one patient refused treatment and 1 was lost to follow-up.

CR = 1 (3%)

PR = 9 (24%)

SD = 13 (34%)

PD = 13 (34%)

OR = 26% (CR + PR) (95%CI: 12-40%)

TCR = 60.5% (CR + PR + SD) (95%CI: 45-77%).

Median response duration = 8.9 months (95%CI: 6.5-11.4)

Median TTP = 4.6 months (95%CI: 2.4-6.8)

Median OS = 18.1 months (95%CI: 5.6-30.6).

Safety:

Grade 3 events (%):

Hand-foot syndrome = 5%

Stomatitis = 3%

Diarrhoea = 3%

Laboratory abnormalities:

Grade 3 events (%):

Leukopenia = 3%

Granulocytopenia = 5%

Grade 4 events (%):

Granulocytopenia = 5%.

Sub-group analysis:

Significant prognostic factors for OS:

1) Status of hormone receptors:

+ve (median OS not reached)

-ve (median OS = 10.7 months) (P = 0.041 univariate or P = 0.015 multivariate analysis).

2) Disease-free survival:

≥ 1 year (median OS = 23.4 months)

< 1 year (median OS = 1.9 months) (P = 0.027 univariate or P = 0.018 multivariate analysis).

3) Refractoriness to anthracycline:

Non-refractory (median OS = 22.2 months)

Refractory (median OS = 5.3 months) (P = 0.020 univariate or P = 0.022 multivariate analysis).

4) Number of involved organs:

1-3 (median OS = 23.4 months)

4-5 (median OS = 8.4 months) (P = 0.004 univariate or P = 0.0021 multivariate analysis).

Significant prognostic factors for TTP:

Disease-free survival, Refractoriness to anthracycline, Number of involved organs. No data presented.

General comments:

This was an open label phase II study, undertaken between September 1999 and December

2002. The aim was to evaluate the efficacy of capecitabine and to determine if there was a sub-group of patients who might most benefit from the intervention.

Recruitment: All patients had MBC and were recruited from a single secondary care facility in South Korea. There was a great variety in the degree of metastatic disease, number of sites and previous therapy etc which probably made this study group representative of the MBC population as a whole.

All patients had previously failed taxane (palliative) and anthracycline (palliative or adjuvant) therapy.

Compared with other similar observational studies, the exclusion criteria in this study are quite stringent. Exclusion of patients with other malignant disease or clinically significant cardiac disease etc will obviously bias toward selection of patients with a better prognosis.

Allocation: The treatment regime is clearly outlined. Dose reductions were specified for toxicity.

The authors undertook a sub-group analysis of potential prognostic factors for TCR, TTP and OS. They identified 16 potential factors and used a Cox proportional hazards regression model to examine their impact on each outcome. Only data for OS were presented and these showed that hormone receptor status, length of disease-free survival, anthracycline refractoriness and number of involved organs were all independent prognostic factors. Multivariate analysis showed, not surprisingly, that patients with more favourable levels of these factors had a better overall prognosis but the observed differences between patient groups may well have reflected the natural tumour biology rather than treatment effect.

As there was no comparator group, treatment allocation was not an issue.

Maintenance: A median follow-up period of 27.8 months was reached. There was no discontinuation due to adverse events or treatment related mortality. Two patients dropped out from the study - one refused treatment and the other was lost to follow-up.

Since the primary endpoint under study was TCR, rather than OS, all patients were fully assessed since, from the survival curve, it is evident that all had disease progression by the time of writing.

Measurement: The following outcomes were defined: complete response, partial response, progressive disease, stable disease, response rate, tumour control rate, duration of response, time to progression and overall survival.

Complete medical history, physical examination, laboratory tests and imaging were undertaken at baseline and on the first day of each treatment cycle. It was not stated by whom these tests were performed. Such objective tests formed the basis for determination of the primary outcome, TCR.

Although there were clearly identified prognostic factors, without a comparator blinding was not relevant in the final analysis.

TTP and OS were reported with Kaplan-Meier survival analysis. An analysis was also performed to illustrate TCR as a predictor for OS.

Patient data for OS was stratified according to the number of risk factors (prognostic factors) showing that those with a greater number had poorer OS. This indicated to the authors the sub-groups of patients who would, in their opinion, receive most benefit from capecitabine therapy and, by inference, those that would not.

Mackey <i>et al.</i> (2004)
Design: Phase II study (therapy), evidence level: 3 Country: Canada (federal state, Commonwealth Realm)
Inclusion criteria: Adult females with histologically proven MBC deemed 'appropriate candidates for chemotherapy Karnofsky performance score (KPS) ≥ 60% Measurable disease Absolute neutrophil count ≥1500 per µl Platelet count ≥100,000 per µl Haemoglobin ≥ 10g per dl Total bilirubin not greater than the upper limit of normal (ULN) for the institution Creatinine ≤ 1.5 times ULN Previous anthracycline treatment unless contraindicated Written informed consent.
Exclusion criteria: Patients with previous taxane or capecitabine exposure or pre-existing neuropathy defined by WHO grade ≥2
Population: Number of patients = 20. Age range 38 to 70 years, mean age = 53 years
Interventions: All patients received 21-day cycles of oral capecitabine 900 mg per m ² twice daily for 14 days followed by a 7-day rest period plus docetaxel 30 mg/ m ² as a 20 min iv infusion once per week throughout the study. Patients received a maximum of eight treatment cycles. No comparator.
Outcomes: Time to treatment failure (TTF), time to tumour progression (TTP), partial response (PR), objective response (OR), overall survival (OS), stable disease (SD), progressive disease (PD).
Follow up: Assessments were performed after two, five and eight cycles. No details of post-study follow-up, if any, given.
Results: Patient characteristics: KPS = Mean 81.5% (range 60-100) Female reproductive status n (%): Childbearing potential = 6 (30%) Postmenopausal = 14 (70%) Previous systemic therapy n (%): Anthracycline = 18 (90%) Hormone therapy = 14 (70%) Previous chemotherapy n (%): Primary BC = 18 (90%) MBC = 12 (60%) Primary and MBC = 12 (60%) Sites of metastasis (%): Liver = 60%

Bone = 60%
Lymph nodes = 20%
Pleura = 15%. All patients had ≥ 2 metastases.

Efficacy (measured in ITT population):

Before cycle 2, three patients were withdrawn due to illness or PD. Cycle 2 (n=17):

SD = 9 (53%)

PD = 5 (29%)

PR = 3 (18%)

7 patients withdrawn (5 PD and 2 from unacceptable toxicity). Cycle 5 (n=10):

SD = 5 (50%)

PD = 3 (30%)

PR = 2 (20%)

8 patients withdrawn (5 PD, 2 from toxicity, 1 patient died from sepsis). Cycle 8 (n=2):

SD = 1

PD = 1

PR = 0

Estimated median TTF (range 1-168) = 70 days (95%CI: 49-99)

Estimated probability of continuing treatment at 3 months = 37%.

Estimated median TTP (range 14-749) = 182 days (95%CI: 56-463)

Estimated progression free survival at 1 year = 35%.

Median OS (range 14-798) = 574 days (95%CI: 259-687)

Safety:

Grade 3 events (%):

Asthenia = 30%

Diarrhoea = 20%

Hand-foot syndrome = 30%

Nail disorder = 45%

Alopecia = 15%

Increased lacrimation = 5%

Peripheral neuropathy = 5%

Rhinorrhoea = 5%

Nausea = 5%

Taste disturbance = 10%

Mucosal inflammation = 10%

Aggravated nausea = 10%

Laboratory abnormalities:

Grade 4 events n (%):

Neutropenia = 5%

19/20 patients withdrew from the study before completion due to either PD or toxicity. One patient completed the 8 cycle treatment schedule but died from sepsis a few days thereafter.

General comments:

Report includes both phase I (dose-finding) and phase II studies undertaken between Sep 1999 and Jan 2002. The aim of this study was to investigate optimal doses of both components of the docetaxel and capecitabine combined therapy.

Recruitment: All patients had MBC and were recruited from a single secondary care facility in Canada. There was variety in previous treatment, sites of metastatic disease etc which probably made this study group representative of the MBC population as a whole. The sample size is very low.

90% of patients had previously received anthracycline treatment.

Allocation: The treatment regime was clearly outlined. Dose reductions were specified for toxicity. No prognostic factors were identified.

The survival curves for TTP, TTF and OS were drawn for the entire population. The authors state that the observed difference between median TTF and median TTP is attributable to early treatment discontinuation.

As there was no comparator group, allocation concealment is not an issue.

Maintenance: Follow-up details are not given. From the survival data it is apparent that all patients had reached disease progression if not the endpoint for OS.

19 patients discontinued treatment either because of PD or toxicity.

Measurements: The following outcomes were defined: time to tumour progression, time to treatment failure and overall survival.

Tumour response was assessed after cycles 2, 5 and 8 using standard WHO criteria, which were well defined. TTP, TTF and OS were reported with appropriate survival analysis. The median OS has a very wide 95%CI which is probably due to the low patient numbers.

Pierga *et al.* (2004)

Design: Phase II study (therapy), evidence level: 3
Country: France

Inclusion criteria:

Females (and males) with MBC who had enrolled on a compassionate use study. All patients registered on this study were required to have failed taxane therapy and anthracycline therapy (or have anthracycline contra-indicated).

Exclusion criteria:

None stated

Population:

Number of patients = 197. Age range 31 to 88 years, median age = 56 years

Interventions:

Recommended treatment regime was 2500 mg per m² divided into two daily doses for 14 days every 21 days. Treatment may have been discontinued, or the dose reduced, at the physician or patient's discretion and further appropriate treatment may be have been administered. Standard dose reductions were employed in the event of toxicity.

Outcomes:

Primary outcomes: time to progression (TTP) and overall survival (OS).

Secondary outcomes: complete response (CR), partial response (PR), stable disease (SD), and overall response rate (ORR).

Follow up:

Median follow-up by study cut-off: 8.5 months (range: 0.3-24.6)

Results:

Patient characteristics:

Performance status n (%):

0-1 = 109 (60%)
2 = 39 (21%)
≥ 3 = 34 (19%)
NK = 15 (-)

Menopausal at diagnosis n (%):

Yes = 92 (47%)
No = 102 (53%)
NK = 3 (-)

Primary tumour n (%):

T1-2 = 140 (79%)
T3-4 = 38 (21%)
NK = 19 (-)

Scarff-Bloom-Richardson (SBR) grade n (%):

1-2 = 54 (49%)
3 = 57 (51%)
NK = 86 (-)

Hormonal status n (%):

ER +ve = 148 (80%)
PR +ve = 140 (76%)
Both +ve = 68%

Median time from diagnosis to metastatic disease = 44.9 months (range 0.7-331.3)

Median time from metastatic disease to treatment initiation = 34.6 (range 0.3-270.6)

Sites of disease n (%):

Bone = 116 (59%)
Liver = 86 (44%)
Lung = 76 (39%)
Skin = 59 (30%)
Lymph nodes = 52 (26%)
Pleura = 46 (23%)

Chemotherapy n (%):

Adjuvant = 118 (61%)
Palliative = 189 (96%)

Hormonal therapy n (%):

Adjuvant = 67 (35%)
Palliative = 138 (71%)

Number of lines of palliative chemotherapy n (%):

0 = 6 (3%)
1 = 19 (10%)
2-3 = 97 (49%)
≥ 4 = 75 (38%)

Chemotherapy agents n (%):

Taxanes = 158 (81%)
Anthracyclines = 122 (62%)
Vinorelbine = 111 (57%)
5-FU protracted = 28 (14%)
5-FU other = 25 (13%)

Efficacy n (%):
CR = 1 (1%)
PR = 29 (15%)
SD = 66 (34%)
PD = 76 (39%)
Not assessable = 24 (12%)
NK = 1 (1%)
ORR = 15% (95%CI: 11-21%)

Median duration of response = 8.9 months (95%CI: 6.1-11.7)
Median duration of SD = 6.6 months (95%CI: 5.1-8.0)
Median TTP = 4.8 months (95%CI: 4.1-5.0)(n=152)
Median OS = 14.7 months (95%CI: 9.6-19.8)

Safety:
Patients received a median of 5 cycles of treatment. 32% of patients received dose reduction, mostly for toxicity. 32 patients discontinued treatment because of toxicity.

Grade 3-4 adverse events:
Haematological n (%):
Anaemia = 7 (4%) (n=180)
Leukopenia = 11 (6%) (n=180)
Thrombocytopenia = 5 (3%) (n=180)
Febrile neutropenia = 1 (1%) (n=NK)

Gastrointestinal n (%):
Diarrhoea = 12 (7%) (n=174)
Mucositis = 10 (6%) (n=177)
Nausea = 6 (3%) (n=175)
Vomiting = 4 (2%) (n=173)
Hand-foot syndrome = 29 (16%) (n=177)
Asthenia = 15 (9%) (n=159)

General comments:

Study was undertaken between September 1998 and January 2001 in 32 secondary care facilities (some of these centres may have been tertiary).

Recruitment: Patients were recruited onto a compassionate use study. The only criteria were that they should have MBC and no other inclusion or exclusion criteria were enforced. The sample size is high.

122 (62%) patients received anthracyclines and 158 (81%) taxanes, as palliative therapy. It is not recorded how many patients had received both drugs in this setting.

Allocation: The treatment is assumed to be according to license but this is not formally recorded and was only recommended.

Maintenance: Drop-out rates are not recorded in this retrospective data analysis.

Median follow-up period with 95%CI was recorded. Whilst median OS had been reached in the entire study population this was not true of the responding patients who had a significantly longer survival time than non-responders ($P < 0.0001$).

Using univariate and multivariate analysis, the authors identified several prognostic factors of ORR, TTP and OS. Response to treatment was strongly prognostic for OS with non-responders

(SD and not evaluated) having a 5-fold risk of death compared with responders (CR and PR).

Measurement: No patient data were collected or monitored prospectively but rather were extracted from records with the co-operation of treating physicians. Derived data from missing information were not used, with the exception of hormone receptor status, which was assumed to be positive if patients were treated with hormone therapy.

There is an assumption by the authors, having studied case notes, that tumour response was assessed according to WHO criteria and adverse events were graded according to NCI-CTC standards.

Authors detailed the following outcomes: TTP and OS.

It seems likely, given the programme in which these patients were enrolled, that many would have had a poor prognosis and, in the light of this, a low OS and higher TTP might be expected, compared with other studies. The result may, if anything, perhaps underestimate the efficacy of capecitabine as treatment of the MBC population as a whole. Nonetheless, given the high patient number, the fairly wide CI may be reflecting the very heterogeneous background of this study group.

Reichardt <i>et al.</i> (2003)
Design: Observational study (prognosis), evidence level: 3 Country: Germany
Inclusion criteria: Female patients 18-80 years and histologically confirmed MBC. Progression after paclitaxel or docetaxel therapy Karnofsky performance score (KPS) ≥ 60% Life expectancy of ≥ 3 months Absolute neutrophil count (ANC) ≥ 1,500 per µl Platelets ≥ 75,000 per µl Haemoglobin ≥ 9 g per dl Bilirubin <2 x upper limit of normal (ULN) No chemotherapy 3 weeks prior to enrolment Aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase all < 2.5 x ULN except for patients with bone metastases in which up to 5.0 x ULN was permitted.
Exclusion criteria: Patients with hypersensitivity to 5-FU or having received continuous infusion of 5-FU, significant hepatic, renal, cardiac or gastrointestinal disease (not all parameters were detailed).
Population: Number of patients = 136. Age range 32 to 77 years, median age = 56 years
Interventions: Patients received two 21-day cycles of oral capecitabine at 1250 mg per m ² twice daily for 14 days followed by a 7-day rest period. After 6 weeks, if there was a positive tumour response then patients received a further 6 cycles. If positive tumour response was maintained then patients could received a further 16 cycles, therefore a possible maximum of 24 cycles. There was a total of 700 cycles of treatment during the study with a median of 4 cycles per patient (range: 1-33). Patients with intolerable toxicity were withdrawn throughout the study.
Outcomes: Primary: Objective response rate (RR = CR + PR), tumour control rate (TCR = CR + PR + SD)

Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), time to treatment progression (TTP), overall survival (OS), response duration.

Follow up:

Routine, baseline medical assessments were made within 2 weeks before the start of the treatment and laboratory tests were evaluated within 1 week. HER2 status was not tested. Laboratory tests were repeated every 3 weeks, along with safety evaluations. Adverse events were assessed when patients visited the clinic.

Tumour assessments were repeated every 6 weeks after initial examination and at the time of study withdrawal.

Survival data were collected every 3 months after patients left the study.

Median follow-up = 10 months (range 0.4-31)

Results:

Patient characteristics:

KPS n (%):

60% = 5 (4%)

70% = 10 (7%)

80% = 26 (19%)

90% = 61 (45%)

100% = 33 (24%). Median = 90% (range 60-100)

Time between initial diagnosis and study enrolment:

Median = 3.9 years (range 0.2-27.3)

Time between initial diagnosis and first metastases:

Median = 1.8 years (range 0.0-20.5)

Tumour grade on Scarfe and Bloom scale n (%):

Grade NK/1 = 19 (14%)

Grade 2 = 42 (31%)

Grade 3 = 74 (54%)

Estrogen receptor status n (%):

NK = 12 (9%)

Positive = 72 (53%)

Negative = 52 (38%)

Progesterone status n (%):

NK = 12 (9%)

Positive = 70 (51%)

Negative = 54 (40%)

Site of metastases (%):

Liver = 53%

Lung = 25%

Bone = 42%

Skin = 25%

Lymph nodes = 16%. Median no. of metastases = 2 (range 1-8)

Number of patients pre-treated with anthracyclines = 127 (93%) or taxanes 134 (99%)

Efficacy (measured in ITT population):

CR = 2 (1%)

PR = 19 (14%)

SD = 63 (46%)

TCR = 62% (95%CI: 53-70)

RR = 15% (95%CI: 10-23)

PD = 52 (38%) with 12 weeks of treatment

Median TTP = 3.5 months (95%CI: 2.8-4.1)

Median OS = 10.1 months (95%CI: 8.2-11.5). For patients achieving CR or PR median survival was 21.6 months (95%CI: 13.8-27.9) compared to patients with SD and a median survival of 106 months (95%CI: 8.5-14.3) or PD at 5.5 months (95%CI: 2.7-7.5).

Median response duration = 7.5 months (95%CI: 6-9.2).

Sub-group analyses:

Patient response to capecitabine was analysed according to the outcome of their previous taxane therapy (CR, PR, SD or PD unless given as adjuvant therapy).

Numbers achieving tumour control (CR + PR + SD) with capecitabine:

Of 16 patients given taxane as adjuvant therapy = 9 (56%)

Of 2 patients achieving CR with taxanes = 2 (100%)

Of 36 patients achieving PR with taxanes = 21 (58%)

Of 56 patients achieving SD with taxanes = 36 (65%)

Of 22 patients experiencing PD with taxanes = 15 (68%)

An analysis of response to capecitabine according to previous therapy type received showed that there were no significant prognostic factors.

Safety:

1 patient withdrew from the study before cycle 2 and therefore there is no safety data for this patient. Discontinuation due to toxicity occurred in 17% of patients, after a median of 2 treatment cycles (range 1-20 cycles). There were no treatment related deaths.

Grade 3/4 adverse events (%):

Hand-foot syndrome = 13%

Diarrhoea = 8%

Vomiting = 4%

Nausea = 3%

Grade 4 events:

Stomatitis = 1 case

Diarrhoea = 1 case

Myelosuppression = 4 cases

Laboratory abnormalities:

Grade 3/4 events (%):

Thrombocytopenia = 2%

Leukopenia = 1%

General comments:

Study undertaken between March 1999 and September 2001. Interim data were published as abstracts Reichardt *et al* (2000) and Thuss-Patience *et al* (2001) and as Reichardt *et al* (2001), a paper reviewed in the HTA.

Recruitment: All patients had MBC and were recruited from ten secondary care facilities in Germany. There was a great variety in previous treatment, performance status etc which

probably made this study group representative of the MBC population as a whole.

The majority of patients had previously received anthracyclines (93%) and/or taxanes (99%).

The sample size was reasonable - the authors had, from an assumed type I error of 5% and a power of 90%, calculated a sample size sufficient for sub-group analysis.

Allocation: Treatment regime was clearly outlined. Sub-group analysis was performed on the results from 132 patients (97%) to determine the response to capecitabine stratified by previous response to taxane therapy. The authors concluded that the data showed 13% patients responded positively to capecitabine despite having failed taxanes.

A similar analysis of response to capecitabine, stratified according to previous treatment, showed no significant prognostic factors.

As there was no comparator group, allocation concealment was not an issue.

Maintenance: The median overall follow-up was for 10 months, at which time 104 patients had died or had PD, with no distinction between these two groups. One patient was considered to be a study failure, having refused treatment during the first cycle.

The primary objective of the study was to show 'adequate activity of capecitabine' measured by OR rates. All but 4 patients were included in this analysis - two had not received a taxane previously and two had unknown response to their last taxane treatment.

Measurement: The following outcomes were defined: time to response, duration of response, time to progression and survival time.

Full medical assessments were made at baseline and regularly throughout the study. It was not stated by whom these assessments were made. Such objective tests formed the basis for determination of the primary outcome.

Patient data were analysed in sub-groups according to whether or not taxane or 5-FU had been given previously for metastatic disease.

TTP was reported with Kaplan-Meier survival analysis.

TCR was expressed as a rate with 95%CI. OS was reported as a median with 95%CI: which were quite narrow, reflecting the moderate to high sample size in this study.

Wist *et al.* (2004)

Design: Observational study (prognosis), evidence level: 3

Country: Norway

Inclusion criteria:

Female patients ≥ 18 years and ≤ 75 years with histologically or cytologically proven, bidimensionally measurable locally advanced or MBC.

Previous treatment with anthracycline and a taxane (docetaxel or paclitaxel).

ECOG: 0-2

Absolute neutrophil count ≥ 1500 per μl

Platelet count $\geq 100,000$ per μl

Aspartate aminotransferase and alanine aminotransferase ≤ 3 times the upper limit of normal (ULN)

Bilirubin $\leq 1.25 \times \text{ULN}$

<p>Serum creatinine $\leq 1.5 \times$ ULN Written informed consent Life expectancy ≥ 3 months Negative pregnancy test required in women of childbearing age Agreement to practice 'appropriate contraception' during trial</p>
<p>Exclusion criteria: Other malignant disease Rapidly progressing visceral involvement History of seizures CNS disorders, including brain metastases Psychiatric disability Unexpected reaction to 5-FU or known sensitivity Significant heart disease Lack of upper GI integrity or known malabsorption</p>
<p>Population: Number of patients = 48. Age range 35 to 74 years, median age = 55 years</p>
<p>Interventions: Patients received 21-day cycles of oral capecitabine 1250 mg per m² twice daily for 14 days followed by a 7-day rest period. Treatment was applied until tumour progression, unacceptable toxicity or at the patient's request.</p> <p>For patients experiencing grade 2 or higher adverse effects a standard dose modification scheme was applied.</p>
<p>Outcomes: Primary: Time to disease progression (TTP)</p> <p>Secondary: Response rate (RR), overall survival (OS), toxicity, duration of response, tumour control rate (TCR), partial response (PR), complete response (CR)</p>
<p>Follow up: Baseline evaluation included recording a complete history, medical examination, full blood count, platelet count, serum chemistry, ECG (optional), bone scan, tumour measurement and assessment.</p> <p>Tumour measurements for response were made every 9 weeks, and these results were confirmed within a further 4 weeks.</p> <p>Only patients completing at least three course of chemotherapy were included for assessment and patients failing to achieve this were considered to be non-responders.</p>
<p>Results: Patient characteristics: Metastatic sites n: Liver = 24 Bone = 18 Lung = 13 Regional lymph nodes = 10 Pleura = 8 Thoracic wall = 7 Skin = 5 Mediastinum = 3 Breast = 1 Abdomen = 1 33 patients had > 1 metastases</p>

TNM staging:

T1 = 13
T2 = 18
T3 = 7
T4 = 5
Tx = 5
N0 = 16
N1 = 27
Nx = 5
M0 = 44
M1 = 4

Hormone receptor status:

ER and or PR +ve = 28
ER and or PR -ve = 20

Her2/neu status:

Her2 +ve = 3
Her 2 -ve = 13
Her2 unknown = 32

Median time since diagnosis = 1520 days (range: 176-7543)

ECOG status n:

0 = 3
1 = 32
2 = 13

Efficacy n (%):

PR = 14 (29%) (95%CI: 16-42)
SD = 16 (33%)
TCR (PR + SD) = 30 (62%)

Median TTP = 107 days (95%CI: 85-129)

Duration of response = 134 days (range 23-534)

Median OS = 282 days (95%CI: 164-398)

Safety:

Grade 2 and 3 adverse events n (%):

Hand-foot syndrome = 17 (35%)
GI toxicity = 11 (23%)
Haematological criteria = 3 (6%)

General comments:

Study undertaken between April 2000 and December 2001.

Recruitment: All patients had MBC and were recruited from a single secondary care centre in Norway. There was great variety in the degree of metastatic disease, number of sites, previous treatment, tumour grade etc. which probably made this group representative of the MBC population as a whole.

All patients had previously failed both anthracycline and taxane treatment.

Compared with other similar observational studies, the exclusion criteria in this study are quite stringent. Exclusion of patients with CNS disorders, other malignant disease and rapidly

progressing involvement of viscera etc will obviously bias toward selection of patients with a better prognosis.

Allocation: The treatments are well described. No prognostic factors were identified. The survival curves for TTP and OS were drawn for the entire study population.

As there was no comparator group, allocation concealment was not an issue.

Maintenance: There are no details of patient follow-up or of possible post-study treatments. Similarly, the number of patients alive at the time of publication is not known.

Measurement: The following outcomes were defined: complete response, partial response, stable disease, progressive disease and duration of response.

It was not stated how many people had died during the course of the study or who were alive at the time of publication. No details were given of disease progression in the remaining population but, from the TTP survival curve, it appears that all patients reached that endpoint.

TTP and OS were reported with appropriate survival analysis. Median values with 95%CI:s are given for both primary outcomes. The intervals are quite wide, reflecting the low to moderate sample size in this study.

Leonard <i>et al.</i> (2002)
Design: Retrospective case series (prognosis), evidence level: 3 Country: United Kingdom
Inclusion criteria: None stated (named patient study) Patients all have metastatic disease.
Exclusion criteria: None stated.
Population: Number of patients = 102. Age range 30 to 95 years, median age = 53 years
Interventions: Patients received 21-day cycles of oral capecitabine at 1000 mg per m ² twice daily for 14 days followed by a 7-day rest period. Treatment was applied until the occurrence of tumour progression or unacceptable toxicity. Adverse events were graded according to NCI, Canada Common Toxicity Criteria. Hand-foot syndrome was graded 1-3. For patients experiencing grade 2 or higher adverse effects a standard dose modification scheme was applied. Patients received a median of 4.5 treatment cycles.
Outcomes: None stated specifically. Kaplan-Meier analysis of time to disease progression (TTP) and overall survival (OS) shown. Other outcomes reported: Complete response (CR), partial response (PR), overall response (OR = CR + PR), stable disease (SD), progressive disease (PD), safety.
Follow up:

At publication 88 patients had progressive disease.

Follow-up period not stated.

Results:

Patient characteristics:

ECOG performance status (n):

0-1 = 61

2-3 = 24

NK = 17

Number of metastatic sites (n):

1-3 = 96

≥ 4 = 6

Metastatic sites (n):

Liver = 37

Lung = 23

Lymph nodes = 62

Bone = 45

Oestrogen receptor status (n):

Positive = 40

Negative = 22

NK = 40

Chemotherapy setting (n):

Neoadjuvant = 21

Adjuvant = 50

Metastatic = 76

Chemotherapeutic agents (n):

Anthracyclines = 62

Taxanes = 26

5-FU = 7

Anthracyclines and taxanes = 22

Hormone therapy setting (n):

Adjuvant = 61

Metastatic = 54

Prior surgery = 89

Prior radiotherapy = 102

Efficacy:

Median duration of response = 6.9 months

Median TTP = 4.1 months

Median OS = 7.7 months

CR = 3% (95%CI: 0-6)

PR = 17% (95%CI: 9-24)

OR = 20% (95%CI: 12-20)

SD = 46% (95%CI: 36-56)

PD = 31% (95%CI: 21-39)

NK = 4% (95%CI: 0-8)

Safety:

At least 20% patients experienced adverse events (mostly mild to moderate - grade not stated) commonly hand-foot syndrome and GI side effects: diarrhoea (33%) and nausea (24%).

Laboratory abnormalities:

3 patients experienced grade 3/4 neutropenia and 1 patient had grade 3 thrombocytopenia.

General comments:

This is a study of a named patient programme, undertaken between August 1998 and February 2001. The aim was to determine efficacy and safety of capecitabine in patients recruited from 21 centres in the UK. It is not clear from the text whether or not this was a prospective or retrospective analysis. Lack of detail suggests the latter.

Recruitment: All patients had MBC and were enrolled on a named patient programme. There were no inclusion or exclusion criteria stipulated as this study was intended to reflect 'real practice conditions' rather than those of a clinical trial setting.

Allocation: The treatment regime is clearly outlined. Dose reductions were applied according to standard criteria.

Maintenance: Follow-up period not stated. At the time of writing 88 patients had disease progression (78%). No other information given.

Measurement: "Tumours were evaluated by the investigator during treatment using standard clinical and/or radiological methods and the best response achieved by each patient was recorded."

Miles *et al.* (2004)

Design: Retrospective case series (prognosis), evidence level: 3

Country: Multi-national

Inclusion criteria:

Female patients ≥ 18 years with histologically or cytologically confirmed breast cancer with unresectable locally advanced and/or MBC

At least one bidimensionally measurable lesion that had not been irradiated, with a minimum size in at least one diameter ≥ 20 mm (liver) and ≥ 10 mm (lung, skin, lymph node) metastases

Recurrence after anthracycline treatment

Karnofsky performance score $\geq 70\%$

Life expectancy ≥ 3 months

Written informed consent.

Full details of inclusion criteria are given in O'Shaughnessy *et al* (2002).

Exclusion criteria:

Previous treatment with docetaxel-containing regimen in adjuvant or advanced disease setting

Previous treatment with three or more previous chemotherapy regimens for advanced or MBC.

Full details of exclusion criteria are given in O'Shaughnessy *et al* (2002).

Population:

Number of patients = 511. Age range 26 to 79 years, median age = 52 years

Interventions:

Patients were stratified according to whether or not they had received prior paclitaxel therapy.

Treatment arm received 21-day cycles of oral capecitabine (1250 mg per m²) twice daily for 14 days followed by a 7-day rest period plus docetaxel (75 mg per m²) as a 1 hour iv infusion on the first day of each 21-day treatment cycle.

Comparator arm received docetaxel (100 mg per m²) administered as a 1 hour iv infusion on day 1 of a 21-day treatment cycle.

Patients showing stable disease or a positive response after 2 cycles of therapy continued until disease progression or unacceptable toxicity.

Patients with progressive disease were administered a range of post-study therapies at the treating physician's discretion. Specific treatment regimes are not outlined in detail.

Outcomes:

Overall survival (OS)

Follow up:

This report details patients after a follow-up period ≥ 27 months, an update on the original paper which reported after 15 months.

Tumour responses were evaluated according to WHO criteria at 6 week intervals until week 48 then at 12 week intervals until disease progression.

Results:

After a minimum follow-up period of 27 months:

Median OS for CAP/DOC = 14.5 months (95%CI: 12.3-16.3 after 82% of events)

Median OS for DOC = 11.5 months (95%CI: 9.8-12.7 after 87% of events).

HR = 0.777 (95%CI: 0.645-0.942) P < 0.01

Post-study therapy:

198/256 DOC patients received ≥ 1 post-study treatment. Of these, 28 patients received CAP and 128 patients received other chemotherapy. Patients receiving CAP had median OS = 21 months (95%CI: 15.6-27.6) versus other therapies with median OS = 12.3 months (95%CI: 10.5-14) (HR = 0.5) P = 0.0046

Of the original 255 CAP/DOC patients, 45 had discontinued DOC before progression and continued with single CAP and 34 patients had discontinued CAP before progression and continued with single DOC. Both groups had similar survival: median OS = 18.3 months (95%CI: 14.5-23.4) for CAP versus 15.8 months (95%CI: 9.9-21.5) for DOC (HR = 0.72) P = 0.2

General comments:

Interim data published as Leonard *et al* (2001), Vukelja *et al* (2001), Twelves *et al* (2001) and O' Shaughnessy *et al* (2002) papers that are included in the capecitabine HTA.

This is a retrospective analysis of post-study therapy.

For the purposes of post-study therapy, prior to disease progression, CAP/DOC patients taken off DOC were considered as remaining on combination study therapy but CAP/DOC patients taken off CAP were considered to be receiving DOC as post-study therapy.

Recruitment: In the original study, patients were recruited at a similar stage in their disease and represented the MBC population as a whole.

Allocation: Post-study treatments were fully detailed in the first instance but there were many discrepancies between reported patient numbers in the 'Introduction' compared to the 'Results'

section of this paper which made meaningful interpretation difficult. Personal communication with the lead author revealed that patient drop-out rates had not been reported and hence numbers do not tally between tables, text and graphs.

Maintenance: Clearly, patients were left out of the final analysis but as this is not documented the reasons are not known. Minimum follow-up time was quoted.

Measurement: Post-study treatments were given at the discretion of their clinician. There was no element of blinding etc. This is a retrospective analysis of data.

OS was reported with Kaplan-Meier survival analysis. Median OS was reported with 95%CI: and a hazard ratio with log rank P was calculated between the two arms of post-study chemotherapy treatments.

The authors conclude that the results show a clear survival advantage for patients receiving either CAP/DOC combination therapy or sequential treatment with both agents compared with either as a single agent.

Updated evidence (4.5)

Summary

Additional poor quality evidence on the efficacy and safety of CAP monotherapy comprised three phase II studies (Sezgin *et al.*, 2007, Venturini *et al.*, 2007 and Yap *et al.*, 2007). The treatment outcomes are summarised below, in Table 4.5.3 and data are shown as point estimates and 95% confidence intervals, where given, or data ranges if stated. The most commonly reported adverse events were hand-foot syndrome, diarrhoea and nausea & vomiting.

1st author (study size)	Med ORR %	Med TTP months	Med OS months	Med RD months
Sezgin (n=69)	17	5 (3.2-6.8)	NR	15.4 (11.9-18.2)
Venturini (n=631)	35	6.6 (5.6-7.6)	10 (8.5-15.3)	3.8 (0.1-24.7)
Yap (n=63)	29	18 weeks (range: 2-122)	54 weeks (range: 3-194)	24 weeks (range: 9-68)

Table 4.5.3. Abbreviations: ORR overall response rate, TTP time to progression, OS overall survival, RD response duration, NR Not reported

Two poor quality phase II studies (Mrozek *et al.*, 2006, and Silva *et al.*, 2008) offered limited evidence on CAP + DOC combined therapy which was given at different doses and time intervals between studies. The only outcome reported by both studies was tumour response rate which ranged from 44-50%. Neither study reported median overall survival. The most commonly reported adverse events were neutropenia, diarrhoea and nausea & vomiting.

References

Mrozek E., Ramaswamy B., Young D., Rhoades CA., Kendra K., Allen J., Moore T., Hauger M., Watson H., Merriman N., Nadella P., Villalona-Calero M and Shapiro CL (2006) Phase II study of

weekly docetaxel and capecitabine in patients with metastatic breast cancer. *Clinical Breast Cancer* **7**: 141-145

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Silva O., Lopes G., Morgenzstern D., Lobo C., Doliny P., Santos E., Abdullah S., Gautam U., Reis I., Welsh C., Slingerland J., Hurley J and Gluck S (2008) A phase II trial of split, low-dose docetaxel and low-dose capecitabine: A tolerable and efficacious regimen in the first-line treatment of patients with HER2/neu-negative metastatic breast cancer. *Clinical Breast Cancer* **8**: 162-167

Venturini M., Paridaens R., Rossner D., Vaslamatzis MM., Nortier JW., Salzberg M., Rodrigues H and Bell R (2007) An open-label, multicenter study of outpatient capecitabine monotherapy in 631 patients with pretreated advanced breast cancer. *Oncology* **72**: 51-57

Yap YS., Kendall A., Walsh G., Banerji U., Johnston SR., Smith IE and O'Brien M (2007) Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer--how low can you go? *Breast* **16**: 420-424

Evidence tables

Question: Capecitabine and docetaxel as a combined therapy or capecitabine as a monotherapy
Created by: Karen Francis on 14/07/08

Mrozek <i>et al.</i> (2006)
Design: Phase II study (therapy). Evidence level: 3 Country: United States of America
Inclusion criteria: Aged ≥ 18 years Histologically confirmed breast cancer ECOG status ≤ 2 Measurable lesion Adequate (defined) laboratory parameters Adequate liver and kidney function Written informed consent
Exclusion criteria: More than 2 previous chemotherapy regimes for MBC Treatment with capecitabine (CAP) or docetaxel (DOC) within previous 6 months History of severe hypersensitivity to DOC or polysorbate History of hepatitis B or C, HIV Untreated brain metastases
Population: Number of patients = 39. Age range: 31 to 73 years. Median age = 56 years.
Interventions: [1] DOC at 30 mg per m ² i.v. over 30 min on days 1, 8 and 15 of a 28-day cycle with oral dexamethasone 12 hours before and 12 hours after each DOC infusion [2] Oral CAP at 800 mg per m ² twice a day on days 1-21 of a 28-day cycle Patients received treatment until disease progression, unacceptable toxicity or patient refusal. Dose reductions of DOC and delays were implemented for neutropenic fever or grade 3 non-

haematological toxicity. CAP dosage was modified for grade 4 nausea, grade 3 renal dysfunction or grade 2 hand-foot syndrome or non-haematological toxicity.

Outcomes:

Toxicity, overall response rate (ORR = CR + PR), complete response (CR) partial response (PR) stable disease (SD) progressive disease (PD) time to progression (TTP) response duration (RD).

Follow up:

Baseline assessments included imaging studies, physical examination and tumour evaluation. Toxicity assessments and complete blood counts were obtained on days 1, 8, 15 and 21. Physical examination and serum chemistry studies were obtained on day 1 of each cycle. Tumour response was assessed after every 2 cycles and at the end of treatment.

6 patients received only 1 cycle of therapy (2 patients withdrew, 2 had disease progression and 2 developed grade \geq 3 toxicity and were withdrawn by their physician). 9 patients were withdrawn from the study because of toxicity (2 at grade 4).

Results:

Total number of treatment cycles was 221 with a median of 4 cycles per patient (range: 1-20). 34% of cycles were given at full dose. Data were analysed on ITT principle.

Efficacy (n=39) n:

CR = 4

PR = 13

ORR = 17/37 (44%) (95%CI: 28-60)

SD = 5

PD = 17

Median RD = 9.1 months (95%CI: 6.2-12)

Median TTP = 5.5 months (95%CI: 3.7-7.3)

Grade 3/4 adverse events (n=39) n:

Neutropenia = 6

Anaemia = 1

Asthenia = 7

Diarrhoea = 7

Nausea/vomiting = 5

Stomatitis = 5

Hand-foot syndrome = 4

Infection = 2

Thromboembolism = 1

Lacrimation = 1

General comments:

This paper describes a small phase II study of CAP + DOC combined therapy. 51% of patients had been pre-treated with anthracyclines and 36% with taxane. 82% of patients had visceral metastases. Women were recruited from October 2001 and January 2004 at two treatment centres.

The authors expressed their opinion that this reduced dose of CAP and weekly administration of DOC was shown to be a safe and active regimen having only low incidences of febrile neutropenia and hand-foot syndrome. However, this paper has the usual limitations of a small non-comparative study and hence these conclusions should be viewed with caution.

Sezgin *et al.* (2007)

<p>Design: Retrospective case series (therapy). Evidence level: 3 Country: Turkey</p>
<p>Inclusion criteria: Histological proof of breast cancer Radiographic evidence of metastatic disease One measurable or assessable lesion Previously treated with (or unable to take) anthracycline and taxane for advanced disease Disease progression after chemotherapy</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 69. Age range from 29 to 76. Median age: 52 years.</p>
<p>Interventions: Oral capecitabine (CAP) at 1000 mg per m² twice a day for 14 days in every 21-day cycle. Patients experiencing a complete or partial response after 2 cycles continued therapy until disease progression or unacceptable toxicity.</p>
<p>Outcomes: Objective response (ORR) complete response (CR) partial response (PR) stable disease (SD) progressive disease (PD) response duration (RD) time to tumour progression (TTP).</p>
<p>Follow up: Baseline tests included ECG, chest X-ray, CT of thorax and abdomen, medical history, blood count, physical examination, ECOG status assessment and laboratory tests (blood and serum biochemistry). Complete blood counts and serum tests were repeated at the beginning of each cycle and dose reductions were applied if grade 3 or 4 toxicities were observed. Tumour response, assessed by radiology, was evaluated after every 3 cycles. All patients were evaluated for efficacy and safety. Four patients discontinued treatment due to unacceptable toxicity. There were no treatment related deaths.</p>
<p>Results: Patients received a total of 524 cycles of chemotherapy with CAP with a median of 7.6 cycles (range: 1-26). 46/69 patients received CAP as 3rd line or further. Efficacy (n=69): CR = 0 PR = 12 ORR = 12/69 (17%) Median RD of PR = 15.4 months (95%CI: 11.9-18.2) SD = 32 PD = 21 Median disease stabilisation = 6 months (95%CI: 3.28-8.72) Median TTP after 18 months = 5 months (95%CI: 3.2-6.8) Poor performance status was correlated with shorter TTP. Grade 3/4 adverse events (n=69) / n: Hand-foot syndrome = 6 Fatigue = 3 Anorexia = 2 Dyspepsia = 2 Nausea = 1 Diarrhoea = 1</p>

<p>Conjunctivitis = 1 Infection = 1 Anaemia = 1 Increased bilirubin = 1 Toxic hepatitis = 1</p>
<p>General comments: This paper presents the results of a small retrospective review of case files from 20 women with breast cancer who, having experienced disease progression after anthracycline and taxane therapy, were given reduced dose capecitabine. Patients had been treated between December 2000 and December 2003 at two oncology clinics. 75% of patients had visceral metastases.</p> <p>The authors conclude from these data that CAP at a reduced dose may avoid more commonly experienced adverse events whilst providing an effective and safe option for the treatment of MBC. This appear provides only very limited evidence as a retrospective review of a no-comparative therapy.</p>

<p>Venturini <i>et al.</i> (2007)</p>
<p>Design: Phase II study (therapy). Evidence level: 3 Country: Italy</p>
<p>Inclusion criteria: Women aged ≥ 18 years KPS ≥ 60% Bidimensionally measurable disease Histologically confirmed breast cancer Progressive locally advanced or metastatic disease Pre-treatment with ≥ 2 chemotherapy regimes for metastatic disease, one of which was a taxane Written informed consent</p>
<p>Exclusion criteria: Rapidly progressive visceral disease Prior severe or unexpected reaction to 5'-FU History of seizures CNS disorders Neurological or psychiatric disorders interfering with compliance or informed consent Significant cardiac disease or myocardial infarction within 12 months Malabsorption syndrome Lack of integrity of upper GI tract Pregnant or nursing.</p>
<p>Population: Number of patients = 631. Age range: 47 to 91 years. Median age = 54.1 years.</p>
<p>Interventions: Oral capecitabine (CAP) at 1,250 mg per m² two times a day for 14 days of a 21-day cycle. Dosages could be altered at the discretion of the treating physician according to each patient's circumstances. Treatment responders could continue for up to 16 cycles. Treatment was continued until disease progression, patient withdrawal or unacceptable toxicity.</p> <p>Dose modifications and treatment delays were employed in cases of > grade 2 toxicity.</p>
<p>Outcomes: Adverse events, time to progression (TTP) overall response rate (OOR = CR+PR) complete response (CR) partial response (PR) stable disease (SD) disease progression (PD) time to treatment failure (TTF) overall survival (OS).</p>

Follow up:

All patients receiving at least 1 dose of CAP were eligible for safety assessment. Tumour response was assessed after 6 weeks of treatment using clinical and radiological methods and then re-evaluated after 12 weeks and when the patient left the study. ECG, chest X-rays and CT scans were performed 'regularly' (no further details).

CAP was discontinued in 134 patients due to treatment related adverse events. During the study 161 patients died of which 82 were either within 28 days of therapy and/or described as treatment related.

Results:

The mean or median number of treatment cycles is not recorded but the mean duration of treatment was 3.8 months (range: 0.1-24.7).

Efficacy (n=349):

CR = 10

PR = 111

ORR = 121/349 (34.7%)

SD = 163

PR = 65

The disease response was similar in those patients with or without distant metastases and across different age groups although younger patients (30-40 years) had fewer positive responses but higher levels of stable disease.

Grade 3/4 adverse events /n:

Hand-foot syndrome = 48

Diarrhoea = 57

Nausea = 11

Vomiting = 17

Fatigue = 4

Mucositis = 12

Abdominal pain = 7

Stomatitis = 7

Anorexia = 3

Grade 3/4 haematological events: 3/4 %:

Anaemia = 1.1/0.2

Leukopenia = 0.5/0.2

Lymphocytopenia = 0.2/0

Neutropenia = 1/0.5

Platelet abnormalities = 0/0.2

Thrombocytopenia = 1.4/0.5

Median TTP (n=604) = 6.6. months (95%CI: 5.6-7.6)

Median OS (n=569) = 10 months (95%CI: 8.5-15.3)

Median TTF (n=553) = 3 months 995%CI: 2.8-3.5)

General comments:

This paper describes a large multi-national (14 countries) open access program in which 631 women received third line (or higher) CAP monotherapy at a time before its approval and availability. 94% of patients had metastatic disease. A substantial proportion of patients had comorbidities including cardiac, gastrointestinal and metabolism and nutrition disorders. 77.9% of patients had received prior anthracyclines and 78.7 had received taxanes.

The main outcome of interest to the authors was that of safety and they concluded that CAP was well-tolerated and effective as a therapy for women pre-treated for advanced disease. Most

treatment related toxicities GI symptoms and hand-foot syndrome, mostly of mild or moderate severity. It was noted that some patients had not been given the CAP at the stated dose since this was at the discretion of the physician according to patient status. In addition, formal follow-up evaluation was not mandatory thus explaining the low proportion of evaluable patients from the trial as a whole. The flexibility of this study highlights the need for caution when interpreting the results.

Yap <i>et al.</i> (2007)
Design: Retrospective case series (therapy). Evidence level: 3 Country: UK
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 63. Age range = 30 to 79 years. Median age = 57 years.
Interventions: Oral capecitabine (CAP) at 1000 mg per m ² twice a day for 14 days in every 21-day cycle. Patients experiencing a complete or partial response after 2 cycles continued therapy until disease progression or unacceptable toxicity.
Outcomes: Overall response rate (ORR = CR + PR) complete response (CR) partial response (PR) stable disease (SD) clinical benefit rate (CBR = ORR + SD) disease progression (PD) time to progression (TTP) response duration (RD) overall survival (OS) and toxicity.
Follow up: Patients were followed up until January 2006. Only 48/63 patients had evaluable disease and were included in the efficacy analysis. Four patients stopped CAP after ≤ 2 cycles due to treatment related toxicity but there were no treatment related deaths. At the time of last follow-up 44% of patients were alive.
Results: The median number of cycles given was 5 (range: 1-40). 37% of women had dose reductions due to grade 2 or higher toxicity, most commonly hand-foot syndrome. Efficacy (n=48): CR = 1 PR = 13 ORR = 14/48 (29%) RR for chemotherapy naïve patients = 5/15 (33%) RR for those having received prior chemotherapy = 9/33 (27%) SD = 13 CBR = 27/48 (56%) PD = 21 Median RD = 24 weeks (range: 9-68) Median TTP = 18 weeks (range: 2-122) (23 women had TTP > 6 months) Median OS from the start of CAP = 54 weeks (range: 3-194).

<p>Grade 3/4 adverse events /n: Hand-foot syndrome = 9 Fatigue = 3 Diarrhoea = 4 Neutropenia = 3 Febrile neutropenia = 1</p>
<p>General comments: This paper presents the findings from a retrospective review of case files of women who were given capecitabine (CAP) as first line therapy for advanced breast cancer outside of a clinical trial setting. Patients were treated in one UK centre between April 2001 and April 2005 and 71% had previously received adjuvant or neoadjuvant chemotherapy (52% with anthracyclines and 22% with taxanes).</p> <p>This is a retrospective, non-comparative study of reduced dose CAP and is of limited evidential value but the authors concluded that this lower than usual dosing regime resulted in prolonged TTP with minimal toxicity as a first line therapy for those patients with predominantly soft tissue or bone disease.</p>

<p>Silva <i>et al.</i> (2008)</p>
<p>Design: Phase II study (therapy). Evidence level: 3 Country: United States of America</p>
<p>Inclusion criteria: Histologically or cytologically confirmed MBC Her2 –ve tumour Measurable disease (outside of any radiation port if RT used for MBC) Bone only disease was permitted if assessed by radiography Diagnosis of MBC ≥ 6 months after last adjuvant chemotherapy ECOG 0-2 Adequate (defined) organ function Written informed consent</p>
<p>Exclusion criteria: Other malignancies unless diagnosed > 5 years before enrolment Pregnant or lactating Pre-menopausal (unless willing to undergo adequate contraception) History of severe allergic reaction to compounds similar to DOC, CAP or polysorbate 80 Comorbidity that would endanger patient ≥ grade 2 peripheral neuropathy from any cause</p>
<p>Population: Number of patients = 37. Age range: 36-75. Median age = 55 years.</p>
<p>Interventions: [1] DOC at 25 mg per m² i.v. on days 1 and 8 of a 21-day cycle [2] Oral CAP at 750 mg per m² twice a day on days 1-14 of a 21-day cycle</p> <p>Patients received treatment until disease progression, unacceptable toxicity or patient refusal. Dose reductions of both CAP and DOC were implemented for most adverse events including ≥ grade 3 toxicity and (for CAP) severe hand-foot syndrome. Treatment was continued until disease progression, grade 3/4 toxicity or patient withdrawal.</p>
<p>Outcomes: Overall response rate (ORR = CR + PR), complete response (CR) partial response (PR) stable disease (SD) clinical benefit rate (CBR = ORR + SD) disease progression (PD) time to treatment</p>

failure (TTF) overall survival (OS) and toxicity.

Follow up:

Baseline evaluation included complete medical history, physical examination, tumour measurement and performance status, complete blood count and serum chemistries. Imaging studies were done within 2 weeks of enrolment. Medical history and physical examinations were repeated every 3 weeks. Blood and serum chemistry tests were repeated on days 1 and 8 of each cycle. Imaging was repeated every 2 cycles.

2 women withdrew consent before receiving treatment and were excluded from all analyses. At the time of the analysis 35/39 women were off the study: 4 women withdrew consent, 3 were lost to follow-up, 5 experienced toxicity and 23 had disease progression.

Results:

A total of 329 cycles were administered with a median of 6 cycles per patient (range: 1-50).

Efficacy (n=32) n:

CR = 1

PR = 15

ORR = 16/32 (50%) (95%CI: 33-67)

SD = 6

CBR = 22/32 (68.8%) (95%CI: 53-85)

PD = 10

Efficacy ITT (n=37) n:

CR = 1

PR = 15

ORR = 16/37 (43.2%) (95%CI: 28-59)

SD = 6

CBR = 22/37 (59.5%) (95%CI: 44-75)

PD = 15

Median TTF (at follow-up of 25 months) = 4.25 months (95%CI: 1.5-7)

Median OS not yet reached.

Grade 3/4 adverse events (n=37) n:

Anaemia = 1

Leukocytopenia = 1

Neutropenia = 1

Diarrhoea = 1

Alopecia = 1

Peripheral neuropathy = 3

PPE = 2

Rash = 1

Nail changes = 1

Epiphora = 1

Gastric perforation = 1

Enthesopathy = 1

General comments:

This paper describes a well reported but small phase II series of treatment with split low-dose DOC with low dose CAP as first line therapy in women with previously untreated Her2 –ve MBC. Women were enrolled between November 2003 and March 2006 at a single institution.

The authors admitted that, statistically, findings fell short of a definition of an active regime but that the efficacy results matched those seen in similar trials with mild to moderate adverse events. This study, like other phase II trials, is small and non-comparative and offers evidence of

only very limited value.

4.6 Taxanes as first or second line therapy

Short summary

There was good quality evidence on the use of taxanes as first or second line monotherapy or in combination, comprising a high quality Cancer Care Ontario guideline (Verma *et al.*, 2003), two good systematic reviews (Gherzi *et al.*, 2005 and Bria *et al.*, 2005) and three RCTs (Lin *et al.* 2003, Cassier *et al.* 2008 and Jones *et al.*, 2005). The total patient number exceeded 14,800.

Anthracycline naïve women did not derive any benefit from paclitaxel (PAC) as first line monotherapy compared with controls. A large systematic review found that for anthracycline naïve patients, when taxanes were added to anthracycline based regimes, there were no significant differences in time to progression (TTP) or overall survival (OS) but tumour response was significantly improved. However, PAC and doxorubicin (DOX) combined therapy resulted in superior median OS and TTP compared with cyclophosphamide, 5'-FU and DOX. There was no evidence to suggest a significant difference in quality of life between DOC and PAC when either was combined with anthracycline as first line therapy.

Meta-analysis demonstrated significant improvements in TTP, tumour response and time to treatment failure in favour of taxane containing regimes compared with non-taxane containing regimes and a borderline advantage in OS. However, statistical significance for OS and TTP was lost when only first line therapy with taxanes was considered. Taxanes and taxane-containing regimes were reported to have a higher incidence of neurotoxicity and leukopenia but fewer cases of nausea and vomiting than controls.

PAC monotherapy was preferable to mitomycin in terms of TTP but not other outcomes. DOC monotherapy correlated with improved OS (compared with combined mitomycin and vinblastine) and improved TTP and tumour response compared with several other multi-agent therapies. Good RCT data demonstrated a significant advantage in OS, TTP and response duration for patients on DOC versus PAC monotherapy although the tumour responses were similar. Another RCT found no significant differences in efficacy or survival outcomes between PAC and DOC as first line therapy combined with DOX then given as monotherapy.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with breast cancer	Paclitaxel either alone or in combination with other drugs as part of a chemotherapy regimen Docetaxel either alone or in combination with other drugs as part of a chemotherapy regimen	Standard chemotherapy regimen for advanced breast cancer (e.g. CMF, anthracyclines, mitozantrone, mitomycin)	<ul style="list-style-type: none"> • Overall response • Progression-free survival • Overall survival • Symptom relief • QOL • Adverse events

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

Taxanes alone or combined with other agents for first- or second-line chemotherapy

The evidence base for this update includes a high quality Cancer Care Ontario (CCO) guideline, a Cochrane systematic review, one other systematic review and two RCTs. There was minimal overlap in studies selected for inclusion in the different reviews. The total patient number across studies was in excess of 14,600.

The CCO guideline (Verma *et al.*, 2003) examined the taxanes as first or second line therapy for metastatic breast cancer, reviewing data from seventeen RCTs (n = 5,689) which were identified by literature searches up to July 2002. The results were categorised by taxane and by anthracycline exposure as follows:

Paclitaxel in anthracycline-naïve patients

Six trials assessed survival, only one of which determined an advantage with the use of paclitaxel versus control - patients treated with paclitaxel plus doxorubicin experienced significantly superior median overall survival (OS) and median time to progression (TTP) compared with patients treated with 5'-fluorouracil, doxorubicin and cyclophosphamide. Two other studies reported statistically significant improvements in median progression-free survival (PFS), or time to treatment failure (TTF), when doxorubicin was compared with paclitaxel or combined paclitaxel and doxorubicin was compared with either agent alone. Three trials found higher response rates in parallel with these findings, all of which reached statistical significance. One study found that there was no significant difference in response rates between epirubicin with paclitaxel when compared with epirubicin and cyclophosphamide and, similarly, another study did not detect significant differences in either response rate or survival with these regimes.

Docetaxel in anthracycline-naïve patients

Out of four trials, only one reported on survival and tumour response and showed that there was no significant difference between doxorubicin and docetaxel given to patients who had received prior alkylating agents and no more than one line of chemotherapy for advanced or metastatic disease. Two trials reporting on TTP could detect no difference between regimens with or without docetaxel but three trials reported significantly higher response rates with such docetaxel containing therapies.

Paclitaxel in anthracycline-resistant patients

Two small phase II studies investigated differences between paclitaxel and mitomycin or capecitabine. In terms of response rate there was no significant differences between any comparators. Median TTP was significantly longer for patients on paclitaxel compared with mitomycin but not capecitabine and there was no difference in median OS between paclitaxel and mitomycin.

Docetaxel in anthracycline-resistant patients

Three trials compared docetaxel with other combined chemotherapies and a fourth trial examined docetaxel monotherapy compared with docetaxel and capecitabine combined. All participants had received prior anthracycline therapy. In two of the trials comparing docetaxel with non-docetaxel combined therapies, one detected a significant difference in median OS in favour of docetaxel (compared with mitomycin and vinblastine combined) and the other did not (compared with methotrexate and 5'-fluorouracil). Two of the three trials detected significantly longer times to disease progression and higher response rates with docetaxel than with multi-agent chemotherapy. The third trial's data were incomplete in this respect. Compared with docetaxel monotherapy, treatment with docetaxel and capecitabine resulted in longer duration of survival, PFS and tumour response.

Eight of nine trials reporting on quality of life did not detect statistically significant differences between treatment groups on changes from baseline in measures of quality of life.

Key evidence (taken directly from Verma *et al.*, 2003)

Anthracycline-naïve patients

- Seven randomized trials assessed the use of paclitaxel in anthracycline-naïve patients and four randomized trials investigated the use of docetaxel in this setting.
- One randomized trial evaluated the use of single agent docetaxel versus doxorubicin. The trial reported a higher response rate and less febrile neutropenia, stomatitis, and nausea/vomiting with docetaxel than with doxorubicin monotherapy.
- Evidence from the three randomized trials of single-agent paclitaxel versus doxorubicin-based chemotherapy was conflicting.
- Paclitaxel or docetaxel, in combination with doxorubicin, was associated with higher response rates compared to standard anthracycline combinations in three randomized trials and longer time to disease progression and survival in one trial. Such therapy, however, was associated with higher rates of grade 3/4 neutropenia and neuropathy compared to standard anthracycline regimens.

Anthracycline-resistant patients

- Four randomized trials evaluated the use of docetaxel for anthracycline-resistant metastatic breast cancer and two small randomized trials investigated the use of paclitaxel in this setting.
- One of two small randomized trials detected improved time to progression with paclitaxel compared to non-taxane-containing chemotherapy. The other trial reported no significant difference in time to progression.
- Two of three randomized trials that compared docetaxel with non-taxane-containing chemotherapy detected improved response rates and time to progression with docetaxel, while the third reported no significant difference for these outcome measures. One trial also detected a significant survival advantage with docetaxel compared to mitomycin/vinblastine. The other trial that reported survival data did not detect a significant survival difference.
- One randomized trial that compared docetaxel plus capecitabine to docetaxel alone demonstrated a superior response rate, time to progression, and survival rate for the combination, with high rates of toxicity in both treatment arms.

The Cochrane review (Ghersi *et al.*, 2005) was a high quality review of twenty-one eligible trials (n ~6,300) which compared taxane-containing therapies with non taxane-containing therapies for the treatment of advanced (metastatic) breast cancer. Data were sub-grouped by the nature of the study design e.g. single vs combined chemotherapy but were also presented across all studies by outcome. Data were not sub-grouped by taxane as per Verma *et al.* (2003).

The pooled data came from trials of very varied design - the statistical heterogeneity which was observed may have arisen, for example, because of the different treatment regimens in the comparator arms of individual studies. The authors' conclusions that taxane-containing therapies are better than some, but not all, non taxane-containing therapies may be an acknowledgment of this heterogeneity. Using a random-effects model does not adjust for these differences which must therefore be borne in mind when considering the apparent significance of results. The data across all studies was presented only for assessable patients – an ITT analysis was performed for sub-groups.

Overall survival

Across all studies, the hazard ratio for OS was 0.93 (95%CI: 0.86-1.00 P = 0.05) which is of borderline significance in favour of taxane-combining regimens compared with non-taxane regimens. When only data from those studies comparing regimens for first-line treatment were combined, the findings lost statistical significance. There was no between-studies heterogeneity.

Time to progression

Across all studies, the hazard ratio for TTP was 0.92 (95%CI: 0.85-0.99 P = 0.02) – a significant advantage in favour of taxane-containing regimens but with the caveat that there was significant between-studies heterogeneity ($I^2 = 83.9\%$). Again, looking only at data for first-line therapy, the results lost significance but the between-studies heterogeneity remained ($I^2 = 75.0\%$).

Tumour response

The pooled data for assessable patients suggested a statistically significant advantage of taxane-containing regimens for tumour response (OR = 1.34 95%CI: 1.18-1.52 P < 0.00001) although the between-studies heterogeneity was also significant ($I^2 = 72.99\%$). The data for first-line therapy showed similar results (OR = 1.28 95%CI: 1.10-1.50 P = 0.002) with significant heterogeneity between studies ($I^2 = 85.2\%$).

Time to treatment failure

Taxane-containing regimens showed a statistically significant advantage over non taxane-containing regimens with regard to the median TTF (HR = 0.79 95%CI: 0.71-0.88 P < 0.0001) and with no significant between-studies heterogeneity.

The QOL and toxicity data were reported in tabular and in narrative form. Briefly, when data from studies examining taxane-containing combination therapies vs non taxane-containing controls were pooled, the taxane-containing arm reported significantly higher incidences of neurotoxicity and leukopenia but fewer of nausea and vomiting. Only neurotoxicity was significantly higher when taxane monotherapies were compared with non taxane-containing controls.

A second systematic review (Bria *et al.*, 2005) pooled results from seven trials (n = 2085) that had compared taxane-containing, anthracycline based therapies with non taxane-containing, anthracycline based therapies. The primary outcome was TTP which showed no clear advantage for taxane- anthracycline combined therapy and, similarly, pooled data showed no significant difference between interventions and comparators for OS. However, tumour response was significantly different between arms in favour of taxane-containing therapies (P < 0.001) by either method of data analysis (using median time to event data or log of relative risk) as was the increase in CR of between 81-104% depending on method (P < 0.001).

The taxane-anthracycline combined therapy carried a significantly higher risk of neutropenia than comparator therapies, with a relative risk of between 2.82 and 3.44 (P < 0.001) but it was noted that there was also significant between-studies heterogeneity (P < 0.01). The authors concluded that, despite the higher haematological toxicity, the combination of an anthracycline and a taxane might be an active chemotherapy for patients with MBC. Although this was a very thorough analysis, much of the data for it came from abstracts i.e. unpublished works which were unlikely to have been peer-reviewed.

There were two studies which compared the taxanes as first or second line therapy in women with locally advanced or metastatic breast cancer. Jones *et al.* (2005) presented a RCT (n = 449) comparing docetaxel with paclitaxel as second-line therapy for women with advanced breast cancer (90% with MBC) who had received prior treatment with anthracyclines.

The tumour response in the ITT analysis was not significantly different between treatment arms (DOC = 32% vs PAC = 25%) but median OS (DOC = 15.4 months vs PAC = 12.7 months), median TTP (DOC = 5.7 months vs PAC = 3.6 months) and median RD (DOC = 7.5 vs PAC = 4.6 months) were all statistically significantly superior for the DOC arm participants.

The authors concluded that three-weekly DOC was superior to PAC in TTP, OS, RD and ORR (non-significant) and that the survival advantage was apparent despite higher toxicity in the DOC arm which had led to more dose reductions and withdrawals. The majority of the authors disclosed personal interests in Aventis (manufacturer of docetaxel).

Lin *et al.* (2003) presented a small study of 101 patients who received combination therapy of either docetaxel or paclitaxel with cisplatin for the first or second line treatment of MBC. Prior exposure to anthracycline was a study inclusion, either as neo-adjuvant or adjuvant therapy. Tumour response (DOC + CIS = 62.5% vs PAC + CIS = 42.6), median OS (DOC + CIS = 22.7 months vs PAC + CIS = 22.5 months) and median TTP (DOC + CIS = 9.8 months vs PAC + CIS = 6.5 months) all favoured docetaxel but the results were not statistically significant.

It is not possible to infer that the lack of clear advantage is necessarily because of low patient numbers but a larger study would perhaps have been more conclusive regardless of outcome. In addition, this study, although probably rigorous in its conduct was not well documented with regard to methodology so that although patients were said to have been randomised into two study arms, the complete lack of details about randomisation, allocation etc means that there is a strong possibility of bias.

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Evidence tables

Question: Taxanes as first or second line therapy
Created by: Karen Francis on 24/07/2007

Breast Cancer Disease Site Group <i>et al.</i> (2003)
Design: Guideline (therapy), evidence level: 1++ Country: Canada (federal state, Commonwealth Realm)
Inclusion criteria: Included patients: Women with metastatic breast cancer for whom first- or greater-line chemotherapy is being considered outside the context of a clinical trial. Included studies: RCTs on the use of paclitaxel or docetaxel as single agents or in combination with other chemotherapeutic agents, as first- or second-line chemotherapy, for metastatic breast cancer.

Exclusion criteria: Excluded studies: Letters and editorials
Population: Number of patients = 5689
Interventions: Docetaxel (DOC) or paclitaxel (PAC) alone or in combination other drugs, including anthracyclines, and compared with any other chemotherapeutic agents.
Outcomes: Survival (OS), Time to disease progression (TTP), tumour response (complete response CR, partial response PR), time to treatment failure (TTF), quality of life (QOL), adverse effects.
Follow up: N/A
Results: See Cancer Care Ontario guideline: http://www.cancercare.on.ca/pdf/pebc1-3f.pdf Response and survival Data showing response rate, TTP and OS from RCTs of paclitaxel and docetaxel from 17 included studies: Anthracycline-naïve patients: 1] PAC vs DOX ORR/CR = 2% vs 6% ORR/PR = 25% vs 41%* Median TTP = 3.9 vs 7.5* months Median OS = 15.6 vs 18.3 months 2] PAC vs CMFP ORR/CR = 2% vs 6% ORR/PR = 29% vs 35% Median TTP = 5.3 vs 6.4 months Median OS = 17.3 vs 13.9 months 3] PAC vs DOX vs PAC+DOX ORR/CR = NR ORR/PR = 33% vs 34% vs 46% Median TTP = 5.9 vs 6.2 vs 8.0 months Median OS = 22.2 vs 20.1 vs 22.2 months 4] PAC + DOX vs FAC ORR/CR = 19% vs 8% ORR/PR = 68% vs 55% Median TTP = 8.3 vs 6.2 months* Median OS = 23.3 vs 18.3 months 5] PAC + EPI vs EC ORR/CR = NR ORR/PR = 56% vs 67% Median TTP = NR Median OS = 13.8 vs 13.7 months

6] PAC + EPI vs EC

ORR/CR = 9% vs 6%

ORR/PR = 46% vs 41%

Median TTP = NR

Median OS = NR

7] PAC + DOX vs AC

ORR/CR = 7% vs 3%

ORR/PR = 58% vs 54%

Median TTP = 5.9 vs 6.0 months

Median OS = 20.6 vs 20.5 months

8] DOX vs DOX

ORR/CR = 7% vs 5%

ORR/PR = 48% vs 33%

Median TTP = 6.5 vs 5.3 months

Median OS = 15 vs 14 months

9] 2] DOC + DOX vs AC

ORR/CR = 11% vs 8%

ORR/PR = 60% vs 47%

Median TTP = NR

Median OS = NR

10] DOC + DOX + CYC vs FAC

ORR/CR = 8% vs 5%

ORR/PR = 54%* vs 43%

Median TTP = NR

Median OS = NR

11] DOC + EPI vs FEC

ORR/CR = NR

ORR/PR = 65% vs 37%

Median TTP = 8.4 vs 7.4 months

Median OS = NR

Anthracycline-resistant patients:

12] PAC vs MIT

ORR/CR = 0% vs 0%

ORR/PR = 17% vs 6%

Median TTP = 3.5% vs 1.6 months*

Median OS = 12.7 vs 8.4 months

13] PAC vs CAP

ORR/CR = 0% vs 14%

ORR/PR = 21% vs 36%

Median TTP = 3.4 vs 3.3 months

Median OS = NR

14] DOC vs MIT + VBL

ORR/CR = 4% vs 1%

ORR/PR = 30% vs 12%

Median TTP = 4.8 vs 2.8 months

Median OS = 11 vs 9 months

15] DOC vs MET + 5'-FU

ORR/CR = 9% vs 3%
ORR/PR = 42% vs 21%*
Median TTP = 6.0 vs 3 months*
Median OS = 10.4 vs 11 months

16] DOC vs 5'-FU + VIN

ORR/CR = NR
ORR/PR = 54% vs 44%
Median TTP = 7.0 vs 5.0 months
Median OS = NR

17] DOC vs DOC + CAP

ORR/CR = 4% vs 5%
ORR/PR = 30% vs 42%*
Median TTP = 4.2 vs 6.1 months*
Median OS = 11.5 vs 14.5 months*

* Indicates P < 0.05 between treatment groups.

Abbreviations: 5-FU 5-fluorouracil, AC doxorubicin (Adriamycin)/cyclophosphamide, CMFP cyclophosphamide/methotrexate/fluorouracil/prednisone, EC epirubicin/cyclophosphamide FAC, fluorouracil/doxorubicin (Adriamycin)/cyclophosphamide, FEC fluorouracil/epirubicin/cyclophosphamide, NR not reported.

Paclitaxel in anthracycline-naïve patients

Six of seven trials assessed survival and only one determined an advantage with the use of paclitaxel versus control where patients treated with paclitaxel plus doxorubicin experienced significantly superior median OS (P = 0.013) and median TTP (P = 0.034) compared with patients treated with 5'-fluorouracil, doxorubicin and cyclophosphamide (Jassem *et al.*, 2001). Paridaens *et al.* (2000) and Sledge *et al.* (1997) reported statistically significant improvements in median progression-free survival, or time to treatment failure, when doxorubicin was compared with paclitaxel (P = 0.0001) or paclitaxel and doxorubicin combination therapy was compared with either paclitaxel (P = 0.009) or doxorubicin (P = 0.003) monotherapy. The three trials found higher response rates in parallel with these findings, all of which reached statistical significance. Luck *et al.* (2000) found that there was no significant difference in response rates between epirubicin with paclitaxel when compared with epirubicin and cyclophosphamide. Carmichael (2001) similarly did not detect significant differences in either response rate or survival with these regimes.

Docetaxel in anthracycline-naïve patients

Out of four trials only one (Chan *et al.*, 1999) reported on survival and tumour response showing that there was no significant difference between doxorubicin and docetaxel given to patients who had received prior alkylating agents and no more than one line of chemotherapy for advanced or metastatic disease. Trials reporting on TTP (Chan 1999 *et al.*, 1999 and Bonneterre *et al.*, 2001) could detect no difference between regimens with or without docetaxel but three trials (Chan *et al.*, 1999 and Nabholz *et al.*, 1999, 2001) reported significantly higher response rates with such docetaxel containing therapies.

Paclitaxel in anthracycline-resistant patients

Two small phase II trials (Dieras *et al.*, 1995 and O'Reilly *et al.*, 1998) investigated differences between paclitaxel and mitomycin or capecitabine. In terms of response rate there was no significant differences between any comparators. Median TTP was significantly longer for patients on paclitaxel compared with mitomycin but not capecitabine and there was no difference in median OS between paclitaxel and mitomycin

Docetaxel in anthracycline-resistant patients

Three trials compared docetaxel with other combined chemotherapies (Nabholtz *et al.*, 1999, Sjostrom *et al.*, 1999 and Bonneterre *et al.*, 1997) and a fourth trial (O'Shaughnessy *et al.*, 2002) examined docetaxel monotherapy compared with docetaxel and capecitabine combined. All participants had received prior anthracycline therapy. In two of the trials comparing docetaxel with non-docetaxel combined therapies, one detected a significant difference in median OS in favour of docetaxel (compared with mitomycin and vinblastine combined) and the other did not (compared with methotrexate and 5'-fluorouracil). Two of the three trials detected significantly longer times to disease progression and higher response rates with docetaxel than with multi-agent chemotherapy. The third trial's data were incomplete in this respect. Compared with docetaxel monotherapy, treatment with docetaxel and capecitabine resulted in longer duration of survival (P = 0.0126), progression-free survival (P = 0.0001) and tumour response (P = 0.006).

Quality of life and adverse events

Eight of nine trials reporting on quality of life did not detect statistically significant differences between treatment groups on changes from baseline in measures of quality of life. For full details of this and of adverse events please see the original publication:

<http://www.cancercare.on.ca/pdf/pebc1-3f.pdf>

General comments:

This report includes a systematic review and a practice guideline (developed by the Practice Guideline Initiative's Breast Cancer Disease Site Group). The guideline was appraised using the AGREE tool and found to be of high standard.

This guideline report was reviewed and approved by the Breast Cancer Disease Site Group comprising surgeons, medical oncologists, radiation oncologists, epidemiologists, a pathologist, medical sociologist and patient representative. The report has also been externally reviewed by Ontario practitioners via a mailed survey.

Evidence for the systematic review was searched (including an update) up to July 2002. The databases included in the search were MEDLINE, the Cochrane Library, Physician Data Query database and other databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the San Antonio Breast Cancer Symposium.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiatives Breast Cancer Disease Site Group and methodologists. Because of the between study heterogeneity, in terms of dose, schedule and drug combinations, data were not pooled.

Seventeen RCTs (9 published and 8 in abstract form) were eligible for inclusion in this systematic review of the evidence. One relevant evidence-based practice guideline was found (Guidance on the use of taxanes for the treatment of breast cancer TA30 NICE).

Recommendations (from Verma *et al.*, 2003):

In anthracycline-naïve patients, who would ordinarily be offered treatment with a single-agent anthracycline (doxorubicin or epirubicin) or an anthracycline in a standard combination, the following options are also reasonable:

- Treatment with single-agent docetaxel 100 mg per m² over one hour every three weeks.
- Docetaxel or paclitaxel in combination with doxorubicin.

In anthracycline-naïve patients for whom anthracyclines are contraindicated:

- Treatment with single-agent docetaxel 100 mg per m² over one hour every three weeks is recommended.

In anthracycline-resistant patients or patients who have previously received an anthracycline as adjuvant therapy:

- Either docetaxel (100 mg per m² over one hour every three weeks) or paclitaxel (175 mg per m² over three hours every three weeks) may be considered as a treatment option after failure of prior anthracycline treatment or in women whose disease is resistant to anthracyclines. The evidence supporting the use of single-agent docetaxel is more consistent, and is based on a larger number of trials and patients, than the evidence for paclitaxel.
- In selected patients, the combination of docetaxel and capecitabine is a therapeutic option. Due to the toxicity of the combination, patient selection for good performance status or younger age is recommended. It is recommended that capecitabine in the docetaxel/capecitabine combination be given at 75% of full dose.

The review authors state that the Breast Cancer Disease Site Group agreed with the NICE recommendations from TA30 'Guidance on the use of taxanes for the treatment of breast cancer' but thought that in first-line therapy, taxane-anthracycline combinations could be considered for anthracycline-naïve patients.

References included in the systematic review:

Paridaens R., Biganzoli L., Bruning P *et al.* (2000) Paclitaxel versus doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: a European Organization for Research and Treatment of Cancer randomized study with cross-over. *J Clin Oncol* **18**: 724-33.

Bishop J., Dewar J., Toner G *et al.* (1999) Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front-line therapy in untreated metastatic breast cancer. *J Clin Oncol* **17**: 2355-64.

Sledge G., Neuberg D., Ingle J *et al.* (1997) Phase III trial of doxorubicin vs. paclitaxel vs. doxorubicin + paclitaxel as first line therapy for metastatic breast cancer: An Intergroup Trial [abstract]. *Proc Am Soc Clin Oncol* **16**: 1a.

Jassem J., Piekowski T., Puzaska A *et al.* (2001) Doxorubicin and paclitaxel versus fluorouracil., doxorubicin., and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. *J Clin Oncol* **19**: 1707-15.

Carmichael J. (2001) UKCCCR trial of epirubicin and cyclophosphamide vs. epirubicin and Taxol in the first line treatment of women with metastatic breast cancer [abstract]. *Proc Am Soc Clin Oncol* **20**: Abstract #84.

Luck HJ., Thomssen C., Untch M., Kuhn W., Eidtmann H., du Bois A *et al.* (2000) Multicentric phase III study in first line treatment of advanced metastatic breast cancer. epirubicin/paclitaxel vs epirubicin/cyclophosphamide. A study of the AGO Breast Cancer Group [abstract]. *Proc Am Soc Clin Oncol* **19**: 73a.

Biganzoli L., Cufer T., Bruning P *et al.* (2002) Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicentre Phase III Trial. *J Clin Oncol* **20**: 3114-21.

Chan S., Friedrichs K., Noel D *et al.* (1999) Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* **17**: 341-54.

Nabholtz JM., Falkson G., Campos D *et al.* (1999) A phase III trial comparing doxorubicin and docetaxel to doxorubicin and cyclophosphamide as first line chemotherapy for MBC [abstract]. *Proc Am Soc Clin Oncol* **18**: 127a.

Nabholtz JM., Paterson A., Dirix L *et al.* (2001) A phase III randomized trial comparing docetaxel., doxorubicin and cyclophosphamide to FAC as first line chemotherapy for patients with metastatic breast cancer [abstract]. *Proc Am Soc Clin Oncol* **20**: abstract #83.

Bonneterre J., Dieras V., Tubiana-Hulin M *et al.* (2001) 6 cycles of epirubicin/docetaxel versus 6 cycles of 5FU epirubicin/cyclophosphamide as first line metastatic breast cancer treatment [abstract]. *Proc Am Soc Clin Oncol* **20**: abstract #163.

Dieras V., Marty M., Tubiana N *et al.* Phase II randomized study of paclitaxel versus mitomycin in advanced breast cancer. *Semin Oncol.*, 1995;22 (Suppl 8):33-9.

O'Reilly SM., Moiseyenko V., Talbot DC *et al.* (1998) A randomized phase II study Of Xelodatin (capecitabine) vs paclitaxel in breast cancer patients failing previous anthracycline therapy [abstract]. *Proc Am Soc Clin Oncol* **17**: 163a.27

Nabholtz JM., Senn HJ., Bezwoda WR *et al* (1999) Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. *J Clin Oncol* **17**: 1413-24.

Sjostrom J., Blomqvist C., Mouridsen H *et al.* (1999) Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: a randomised phase III study with crossover on progression by the Scandinavian Breast Group. *Eur J Cancer* **35**: 194-201.

Hakamies-Blomqvist L., Luoma M., Sjostrom J *et al.* (2000) Quality of life in patients with metastatic breast cancer receiving either docetaxel or sequential methotrexate and 5-fluorouracil. A multicentre randomised phase III trial by the Scandinavian breast group. *Eur J Cancer* **36**: 1411-7.

Bonneterre J., Roche H., Monnier A *et al.* (1997) Taxotere versus 5-fluorouracil + Navelbine as second-line chemotherapy in patients with metastatic breast cancer (preliminary results) [abstract]. *Proc Am Soc Clin Oncol* **16**: 162a.

O'Shaughnessy J., Miles D., Vukelja S *et al.* (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* **20**: 2812-23.

Gheri <i>et al.</i> (2005)
Design: Systematic review of RCTs (therapy), evidence level: 1++ Country: Australia
Inclusion criteria: Included studies: Properly randomised clinical trials Included patients: Women with advanced (metastatic breast cancer) either newly diagnosed or recurrent. Women with locoregional disease only were acceptable if they formed less than 20% of the patient group.
Exclusion criteria: Excluded studies: Studies which included women with locoregional disease and whose data were not sub-grouped as such Studies where treatment was given in alternating cycles to investigate sequencing

<p>Excluded patients: Women with locoregional disease only.</p>
<p>Population: Number of patients = ~6,300</p>
<p>Interventions: Intervention: any chemotherapy containing a taxane Comparator: any chemotherapy not containing a taxane Sub-questions: (A) Regimen A plus taxane vs regimen A: e.g. doxorubicin (DOX) + docetaxel (DOC) vs DOX (B) Regimen A plus taxane vs regimen B: e.g. DOX + DOC vs DOX + cyclophosphamide (CYC) (C) Single agent taxane vs regimen C: e.g. DOC vs DOX + CYC</p>
<p>Outcomes: Primary: Overall survival (OS), time to progression (TTP) or progression-free survival (PFS) expressed as hazard ratios (HR) where results < 1.0 favour taxane-containing regimens. Secondary: Tumour response rate - pooled data expressed as relative risk (RR) where results > 1.0 favour taxane-containing regimens, time to treatment failure (TTF), toxicity - pooled data expressed as odds ratio (OR) where results > 1.0 favour taxane-containing regimens, quality of life (QOL).</p>
<p>Follow up: Data for survival was only available for 57% of the total number of trial participants. Data for question C is more complete since 88% of 2,780 women randomised to this question were reported for time-to-event outcomes.</p>
<p>Results: OS (12 trials n = 3643): The HR for overall survival across all studies was 0.93 (95%CI: 0.86-1.00 P = 0.05) in favour of treatment regimens containing taxanes compared with regimens not containing taxanes. There was no significant between-studies heterogeneity ($I^2 = 35.4\%$). If only data for first-line chemotherapy are included, the confidence interval crosses the line of no effect and the findings are non-significant: HR = 0.92 (95%CI: 0.84-1.02) with no significant between-studies heterogeneity ($I^2 = 38.5\%$). When grouped by sub-question: (A) HR = 1.00 (95%CI: 0.82-1.22 P = 1.0). These results were from ECOG E1193 (A) (B) HR = 0.88 (95%CI: 0.76-1.02 P = 0.10). Between-studies heterogeneity was of 'borderline significance' ($I^2 = 60.5\%$). (C) HR = 0.94 (95%CI: 0.86-1.03 (P = 0.2). There was no significant between-studies heterogeneity ($I^2 = 37.9\%$). None of these sub-group results achieved significance. TTP (11 trials n = 3467): The HR for TTP = 0.92 (95%CI: 0.85-0.99 P = 0.02) in favour of treatment regimens containing taxanes compared with regimens not containing taxanes. There was significant between-studies heterogeneity ($I^2 = 83.9\%$). If only data for first-line chemotherapy are included the confidence interval crosses the line of no effect and the findings are therefore non-significant: HR = 0.98 (95%CI: 0.90-1.07). There was also significant between-studies heterogeneity ($I^2 = 75.0\%$). When grouped by sub-question: (A) HR = 0.99 (95%CI: 0.81-1.21 P = 0.94). These results were from ECOG E1193 (A)</p>

(B) HR = 0.81 (95%CI: 0.70-0.94 P = 0.001). There was no significant between-studies heterogeneity.

(C) HR = 0.96 (95%CI: 0.88-1.05 (P = 0.4). There was significant between-studies heterogeneity ($I^2=89.7\%$).

TTF (3 trials)

The HR for TTF = 0.79 (95%CI: 0.71-0.88 P < 0.0001). There was no significant between-studies heterogeneity ($I^2 = 16.7\%$).

Tumour response (15 trials n = 4072)

The OR for tumour response in assessable patients was 1.34 (95%CI: 1.18-1.52 P < 0.00001) in favour of taxane-containing regimens compared with regimens not containing taxanes. There was significant between-studies heterogeneity ($I^2 = 72.99\%$). If data for first-line treatment only are analysed the OR = 1.28 (95%CI: 1.10-1.50 P = 0.002) with significant heterogeneity between studies ($I^2 = 85.2\%$).

When grouped by sub-question:

(A) OR = 1.61 (95%CI: 1.11-2.32 P = 0.01). These results were from ECOG E1193 (A)

(B) OR = 1.70 (95%CI: 1.39-2.08 P ≤ 0.0001). There was no significant between-studies heterogeneity.

(C) OR = 1.08 (95%CI: 0.91-1.28 (P = 0.38). There was significant between-studies heterogeneity ($I^2 = 78.2\%$).

Grade 3/4 toxicity grouped by sub-question:

(A) DOX vs DOX + PAC: leukopenia: 49.6% vs 54.9% respectively, vomiting 6.6% vs 4.5% and lethal toxicity 2.5% vs 1.6%

(B) Pooled results: taxanes were associated with more reports of leukopenia (OR = 2.48 95%CI: 1.75-3.52) and neurotoxicity (OR = 43.11 95%CI: 2.6-714.94) but less of nausea and vomiting (OR = 0.51 95%CI: 0.32-0.80) in assessable patients.

(C) Pooled results: taxanes were associated with more reports of neurotoxicity (OR = 6.61 95%CI: 3.37-12.95) but less of leukopenia (OR = 0.59 95%CI: 0.48-0.74), nausea and vomiting (OR = 0.30 95%CI: 0.20-0.46) and hair loss (OR = 5.27 95%CI: 3.43-8.08) in assessable patients. There were 54 treatment related deaths reported with no significant difference between taxane and non-taxane containing regimens.

Note: the results recorded reflect those from the main text since these differ in some cases both from the meta-analyses and from the summary in figure 3 of the review, presumably as a result of updating.

QOL:

These results were separately reported for each study. Please see table 5 in original review

General comments:

This is a (Cochrane) systematic review of RCTs which compared taxane-containing regimens with non taxane-containing regimens for the treatment of advanced (metastatic) breast cancer in women.

This high quality review was conducted in a very rigorous manner. Several relevant databases were searched up to May 2003 and updated to March 2004, identifying a total of 21 eligible trials. The inclusion criteria were clearly defined (for selection of studies), data extraction was described and the methodological evaluation of included studies was well conducted and reported.

Question A:

Three studies were used to answer this question (ECOG E1193 (A), EU-93011 and SAKK). At the time of publication, the last two trials were still recruiting. On 25th June 2007, the Clinical Trials database showed that the SAKK trial was still active and recruiting but that EU-93011 has

closed but is not published.

Question B:

Nine studies were used to answer this question (306 Study Group, AGO, Bonnetterre *et al.*, Bontenbal *et al.*, CECOG BM1, EORTC 10961, Jassem *et al.*, 2001, Nabholz *et al.*, 2003 and UKCCCR AB01) and all had published data, some of which were presented in abstract form. Complete data for AB01 were not available at the time of publication of this review but are included elsewhere in this document (Langley *et al.*, 2005).

Question C:

Ten studies were used to answer this question (ANZ TITG, 303 Study Group, Dieras *et al.*, 1995 ECOG 1193 (B), EORTC 10923, 304 Study Group, TOG, TXT Group, Talbot and Sjostrom). For particulars of these included studies, please refer to the original paper.

Author's conclusions: When all trials are considered, taxane-containing regimens appear to improve overall survival, time to progression and overall response in women with metastatic breast cancer. The degree of heterogeneity encountered indicates that taxane-containing regimens are more effective than some, but not all non-taxane-containing regimens.

Bria *et al.* (2005)

Design: Systematic review of RCTs (therapy), evidence level: 1+
Country: Italy

Inclusion criteria:

Included studies:

Formal articles in peer-reviewed journals or presented at meetings sponsored by ASCO, ECCO or ESMO

Included patients:

Women with advanced or MBC who were not previously treated.

Exclusion criteria:

None stated

Population:

Number of patients = 2805

Interventions:

Interventions:

Combined anthracycline and taxane regimens: doxorubicin (DOX) + paclitaxel (PAC) or docetaxel (DOC), DOX + 5'-fluorouracil (5'-FU) + DOC or epirubicin (EPI) + PAC or DOC

Comparators:

Anthracycline without taxane: DOX + cyclophosphamide (CYC) with or without 5'-FU or EPI + CYC with or without 5'-FU.

Outcomes:

Primary outcome:

Time to progression (TTP) defined as the time in months from randomisation to disease progression or death from any cause (this is equivalent to progression-free survival in some studies).

Secondary outcomes:

Overall response rate (ORR), overall survival (OS), complete response (CR), neutropenia and febrile neutropenia (FN).

Follow up:

Median follow-up varied between 8.3 months and 49 months depending on outcome and trial.

Results:

A + T regime vs A + non-T regime (method 1: ratio of median times to event):

TTP: RR = 1.10 (95%CI: 1.00–1.21) P = 0.05
ORR: RR = 1.21 (95%CI: 1.10–1.32) P < 0.001
OS: RR = 1.05 (95%CI: 0.90–1.23) P = 0.58
CR: RR = 2.04 (95%CI: 1.41–2.94) P < 0.001
Neutropenia: RR = 1.19 (95%CI: 1.11–1.29) P < 0.001
Febrile neutropenia: RR = 2.82 (95%CI: 1.39–5.69) P < 0.001

A + T regime vs A + non-T regime (method 2: Mantel-Haentzel method using log RR):

TTP: RR = 1.06 (95%CI: 0.99–1.13) P = 0.07
ORR: RR = 1.21 (95%CI: 1.12–1.30) P < 0.001
OS: RR = 1.01 (95%CI: 0.97–1.05) P = 0.51
CR: RR = 1.81 (95%CI: 1.30–2.52) P < 0.001
Neutropenia: RR = 1.15 (95%CI: 1.08–1.23) P < 0.001
Febrile neutropenia: RR = 3.44 (95%CI: 2.44–4.85) P < 0.001

2/7 trials demonstrated a significant benefit for both OS and TTP for anthracycline and taxane combined therapy (Jassem *et al.*, 2001 and Bontenbal *et al.*, 2003) compared with anthracycline without taxanes. One trial showed superior TTP for combined therapy (Nabholtz *et al.*, 2003) but four remaining trials did not reach significance for any survival outcome.

Combined data show that the RR for TTP across studies showed no significant advantage (using method A there is borderline (P = 0.05) significance but method B shows P = 0.07) to taxane-containing therapy.

Combined data show no significant difference between interventions and comparators for OS by either method of calculation. However, tumour response was significantly different between arms in favour of taxane-containing therapies (P < 0.001) by either method as was the increase in CR of between 81-104% depending on method (P < 0.001).

Regarding toxicity, treatment with the taxane-containing regimens resulted in a significant increase in the incidence of neutropenia (between 15% and 19%) (P < 0.001) and febrile neutropenia with RR of 2.82 and 3.44 for methods A and B respectively (P < 0.001).

There was no significant between-studies heterogeneity except for the data concerning neutropenia (P < 0.01) which seems to have made little impact on the results obtained with fixed and random effects modelling.

General comments:

This systematic review was conducted to define the role of taxanes with anthracyclines in first-line treatment with MBC. Data from seven trials were collected and combined.

Databases (including MEDLINE, ASCO, ESMO and FECS but excluding Cochrane or CancerLit) were searched up to December 2003 using search terms outlined in the methods section.

Two methods of data analysis were used. Firstly the data were pooled using the ratio of median times to event, weighted according to sample size, and combined across studies after the method of Simes *et al.* (1987). Secondly, the log of relative risk ratios for time to event data was calculated and applied using both fixed-effect and random-effect models after the method of

Mantel-Haentzel. The results were presented as conventional forest plots. The two methods were comparable for all outcomes and there was no significant between-studies heterogeneity, except in the reporting of neutropenia.

The number of events in time to event analyses was estimated at 6 months assuming an exponential distribution of survival time (found previously to be reliable, at least for TTP where the median TTP was said by the authors to be generally very close to 6 months).

Three of the seven studies included in the review and analyses were not fully published papers but abstracts of unknown quality, providing incomplete results. An inability to adequately grade non-peer reviewed studies does reduce the overall validity of the meta-analysis.

Data were available for TTP in all seven included trials but for 6/7 trials for OS, CR and FN.

Since some of the studies were incomplete, the analyses were performed on data extracted from papers rather than from patients. This introduces a level of inaccuracy which might be reflected in the results and conclusions.

The authors conclude that, despite the significantly higher haematologic toxicity, the combination of anthracyclines and taxanes might be an active chemotherapy for patients with MBC. Both ORR and CR are statistically superior in this respect but there are no obvious advantages in overall survival or time to progression.

Jones *et al.* (2005)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: United States

Inclusion criteria:

Women with locally advanced or MBC who had progressed during treatment with an anthracycline or within 12 months of completing adjuvant or neo-adjuvant therapy

Bidimensionally measurable disease

KPS \geq 60

Neutrophils \geq 2,000 per μ l

Platelets \geq 100,000 per μ l

Total bilirubin < upper level of normal (ULN)

AST and ALT < 3 x ULN if alkaline phosphatase < x 5 ULN

AST and ALT < 1.5 x ULN if alkaline phosphatase < x 2.5 ULN

Creatinine \geq 2 mg per dl

Written informed consent.

Exclusion criteria:

Patients with NCI CTC grade 2 or greater, peripheral neuropathy or history of hypersensitivity to polysorbate 80 or polyoxyethylated castor oil.

Population:

Number of patients = 449

Interventions:

Docetaxel (DOC) at 100 mg per m^2 as a 1hr iv infusion on day 1 of a 21-day cycle (n = 225)

Paclitaxel (PAC) at 175 mg per m^2 as a 3hr iv infusion on day 1 of a 21-day cycle (n = 224)

Both drugs were administered until tumour progression, unacceptable toxicity or withdrawal of patient consent. Dose reductions were employed in the event of toxicity and participants were removed from study if the adverse effects did not resolve satisfactorily.

Therapy with docetaxel was preceded with a 5-day course of oral dexamethasone at 8mg. Paclitaxel was preceded by oral dexamethasone given 6 and 12 hours beforehand, also diphenhydramine and either ranitidine or cimetidine between 30-60 minutes before therapy.

Outcomes:

Primary outcomes: Toxicity, objective response

Secondary outcomes: Time to progression (TTP), overall survival (OS), response duration (RD), QOL.

Follow up:

Baseline tests included radiology, medical history and physical examination. No more than 8 days before study commencement patients were given KPS assessment, ECG, clinical laboratory testing, tumour measurements and neurological examination.

Follow-up included assessment of tumour response after each treatment cycle and radiology after every second cycle. Blood counts were performed weekly for 2 treatment cycles and then before each cycle. Toxicity was graded after each treatment cycle.

Following the study completion patients were followed up every three months. Median follow-up was 5.1 years.

Reasons for discontinuation:

Progressive disease: DOC (47%) PAC (75%)

Adverse events: DOC (25%) PAC (8%) (P<0.01)

Patient withdrawal: DOC (15%) PAC (7%)

Following discontinuation 20% of patients who had been assigned originally to the DOC arm were given PAC and 19% randomly assigned to the PAC arm received DOC. 13% of DOC assignees and 17% of PAC assignees were re-treated with their original taxane.

Results:

The median ages of patients were 56 years (range: 22-93) in the DOC arm and 54 years in the PAC arm (range: 28-82). There were no significant differences between patient characteristics in the two treatment arms - statistical evidence was not offered but tests may have been performed.

The median number of treatment cycles was higher (n = 6) in the DOC arm compared with PAC (n = 4) and the median dose administered per cycle was 95 mg per m² (DOC) or 173 mg per m² (PAC).

Results (ITT population n = 449):

ORR (CR + PR)

DOC = 32% (95%CI: 25.9-38.1)

PAC = 25% (95%CI: 19.3-30.7) nsd

Progressive disease

DOC = 18%

PAC = 30%

Median RD

DOC = 7.5 months (95%CI: 5.8-9.1)

PAC = 4.6 months (95%CI: 3.9-6.0)(P = 0.01)

Median TTP

DOC = 5.7 months

PAC = 3.6 months (HR = 1.64 (95%CI: 1.33-2.02 P < 0.0001))

Median OS
DOC = 15.4 months
PAC = 12.7 months (HR = 1.41 (95%CI: 1.15-1.73 P < 0.03))

Survival at 1 year
DOC = 60%
PAC = 51% (P = 0.096)

Survival at 2 years
DOC = 33%
PAC = 22% (P = 0.009)

Results (assessable population n = 394)
ORR
DOC = 37%
PAC = 26% (P = 0.02)

Median RD
DOC = 7.5 months
PAC = 4.6 months (P = 0.02)

Median TTP
DOC = 5.5 months
PAC = 3.6 months (P < 0.0001)

Median OS
DOC = 16.1 months
PAC = 12.7 months (P = 0.02)

Haematological toxicity (DOC = 222, PAC = 222):
DOC:
Neutropenia = 95.9% (grade 3/4 = 93.3%)
Febrile neutropenia = 14.9%
Anaemia = 77% (grade 3/4 = 10.4%)
Thrombocytopenia = 52.3% (grade 3/4 4.6%)

PAC:
Neutropenia = 83.3% (grade 3/4 = 54.5%) (P < 0.0001 for both)
Febrile neutropenia = 1.8% (P < 0.001)
Anaemia = 61.3% (grade 3/4 = 7.3%) (P < 0.0001 – grade 3/4 was nsd)
Thrombocytopenia = 31.5% (grade 3/4 2.8%) (P = 0.0006 - grade 3/4 was nsd)

Grade 3/4 adverse events (DOC = 222, PAC = 222)/ %:
DOC/PAC:
All events = 55.4/23.0 (P < 0.01)
Pain = 6.3/3.2 nsd
Asthenia = 20.7/5.0 (P < 0.001)
Peripheral oedema = 6.8/0.5 (P < 0.001)
Neurosensory = 7.2/4.1 nsd
Nausea = 5.4/2.7 (P < 0.001)
Stomatitis = 10.8/0 (P < 0.001)
Diarrhoea = 5.4/0.5 (P < 0.001)
Infection = 9.9/1.8 (P < 0.001)
Neuromotor = 5.0/2.3 (P = 0.001)

Myalgia = 2.7/3.2 (P < 0.001)
Skin disorders = 4.5/0 (P < 0.001)
Vomiting = 3.2/0 (P = 0.0002)

There were 4 treatment related deaths (infection = 3, GI bleed = 1) in the DOC arm and none in the PAC arm.

QOL:

FACT-B scores at baseline:

DOC = 45.6 ± 18.7)

PAC = 46.8 ± 20.5) (nsd)

FACT-B scores after cycle 4:

DOC = 48.9 ± 17.8)

PAC = 50.5 ± 19.7) (nsd)

FACT-B scores at study end:

DOC = 54.9 ± 23.0)

PAC = 53.7 ± 22.5) (nsd)

There were no mean changes from baseline to study end for global QOL scores.

General comments:

This multi-centre open label RCT was designed to directly compare the effects of treatment of docetaxel with those of paclitaxel as second line therapy for patients with locally advanced or metastatic breast cancer (90% of patients) who had previously received an anthracycline.

Between October 1994 and October 2001, 449 patients were randomised at 53 institutions in the USA and Canada. The participants were allocated and block randomised at a central location.

Clinical response was monitored by the investigators but results were later reviewed for consistency. It is not stated by whom tumour assessments were performed.

Data were analysed both in assessable patients (those who had received at least one cycle of therapy) and in the intention-to-treat population. Appropriate statistical analyses, including X² test and the Kaplan Meier method, were used to compare categorical and time-to-event data between study arms and prognostic factors were identified using stepwise logistic regression or Cox proportional hazards model.

Significant prognostic factors for OS included DOC therapy (HR = 1.41 95%CI: 1.15-1.73), KPS >70 (P = 0.005), < 12 months from initial diagnosis to first dose (P = 0.003) and fewer involved organs (P = 0.01)

The authors state that three-weekly DOC was superior to PAC in TTP, OS, RD (these results were statistically significant) and ORR (non-significant) and that this survival advantage was apparent despite higher toxicity in this arm which had led to more dose reductions and withdrawals.

The majority of authors disclosed potential conflicts of interest being either employed by, consultant to, or in receipt of honoraria from, Aventis (manufacturer of docetaxel).

Lin *et al.* (2003)

Design: Phase II study (therapy), evidence level: 3

Country: Japan

<p>Inclusion criteria: Women with recurrent or metastatic breast cancer Measurable or evaluable tumour Failure of at least one anthracycline as neoadjuvant or adjuvant palliative chemotherapy WHO status ≤ 2 Age ≥ 18 years Granulocytes ≥ 1500 per μl Platelets $\geq 100,000$ per μl Serum creatinine ≤ 2 mg per dl Transaminase < 5 upper limit of normal Serum bilirubin < 3 mg per dl Written informed consent</p>
<p>Exclusion criteria: Patients with only bony metastases Patients should not have had concurrent major systemic disease or history of other malignancy.</p>
<p>Population: Number of patients = 101 Mean age = 48 years (range: 25-70 years)</p>
<p>Interventions: DOC arm (n = 50): Docetaxel at 60 mg per m^2 iv for 1 hr on day 1 with a 3-day oral dexamethasone pre-medication on day 0 and cisplatin at 50 mg per m^2 iv for 3 hr on day 2 PAC arm (n = 51): Paclitaxel at 175 mg per m^2 iv for 3 hr with iv dexamethasone every 6hr and cimetidine with diphenylhydramine 30 min before therapy on day 1 and cisplatin at 50 mg per m^2 iv for 3 hr on day 2. Dose reductions were given in the event of grade 3/4 toxicity which, if not resolved within 2 weeks, led to withdrawal from the study.</p>
<p>Outcomes: Primary outcome: Overall response rate (ORR), complete response (CR), partial response (PR), stable disease, disease progression (PD) Secondary outcomes: Time to progression (TTP), overall survival (OS), toxicity.</p>
<p>Follow up: Baseline assessment included a complete history review, physical examination, blood counts, biochemistry profile, chest X-ray and bone scans. Before each treatment cycle, toxicity was evaluated and examination, blood count and biochemical profiling were repeated. Imaging was undertaken after four cycles of therapy or if there was suspicion of disease progression. 72.5% patients in the PAC arm stopped therapy due to disease progression (72.5% compared with 40% in the DOC arm). Equal numbers of patient refused treatment due to intolerance. Six patients were excluded from the response assessment due to having bone-only metastases.</p>
<p>Results: Median number of cycles were 6.5 (DOC arm) and 6.4 (PAC arm). Tumour response: DOC arm (n = 48): CR = 6, PR = 24, SD = 7 PD = 11 ORR = 62.5% (95%CI: 48-77) PAC arm (n = 47): CR = 2, PR = 18, SD = 12 PD = 15 ORR = 42.6% (95%CI: 28-57) (P = 0.06) TTP: DOC arm: 9.8 months (95%CI: 7-12.5) PAC arm: 6.5 months (95%CI: 5.4-7) (P = 0.07)</p>

1 year PFS:
DOC arm: 32.3%
PAC arm: 9.8% (P = 0.15)

Median OS:
DOC arm: 22.7 months (95%CI: 19-26.4)
PAC arm: 22.4 months (95%CI: 16.1-28.7) (P = 0.63)

Survival at 1 year:
DOC arm: 77.2%
PAC arm: 63.9%

Grade 3/4 adverse events: DOC/PAC n/n:
Neutropenia = 9/6
Anaemia = 3/10
Nausea/vomiting = 4/7
Mucositis = 4/0
Neuropathy = 3/5
Myalgia = 0/3
Asthenia = 2/1

General comments:

This was a relatively small but well conducted study comparing paclitaxel versus docetaxel, both combined with cisplatin. Although the methodology was carefully detailed in most respects, there was no mention of the randomisation of patients which was stated to have been performed.

Treatment arms were matched and had no significant differences, except for the number of patients with unknown Her2 status (higher in the DOC arm: 20% vs 7% P = 0.0259).

Patients were recruited between April 2000 and December 2002.

Although the results appear to confer an advantage of docetaxel and cisplatin combination over paclitaxel and cisplatin, none of the outcomes were statistically significant. The docetaxel was given at less than the dose seen in other publications because, the authors explain, the clearance rate in the Chinese ethnic group is slower and presumably toxic effects higher. This issue may be relevant when considering external validity i.e. the applicability of this study to the target population of the guideline.

Updated evidence 4.6

Summary

There was only one further paper to update the evidence on taxanes as a monotherapy or in combination with other agents. This RCT (Cassier *et al.*, 2008) compared first line docetaxel (DOC) with paclitaxel (PAC), each combined with doxorubicin and then, after four cycles, given as monotherapy. The primary outcome was quality of life (QOL) which was found not to be significantly different between study groups despite the different toxicity profiles for the taxanes. Secondary outcomes including efficacy and survival were also not significantly different between study arms. Despite the trial being thoroughly conducted there were concerns that bias may have been introduced both from the lack of detail of methodology and also because the QOL questionnaires were self administered. Those women who were in poorer health may have been less likely to have complied with the assessment tool and have therefore excluded themselves from the analysis.

Reference

Cassier PA., Chabaud S., Trillet-Lenoir V., Peaud PY., Tigaud JD., Cure H., Orfeuvre H., Salles B., Martin C., Jacquin JP., Agostini C., Guastalla JP., Perol D and Bachelot T (2008) A phase-III trial of doxorubicin and docetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: results of the ERASME 3 study. *Breast Cancer Res Treat* **109**: 343-350

Evidence tables

Question: Taxanes as first or second line therapy
 Created by: Karen Francis on 24/07/2008

Cassier <i>et al.</i> (2008)
Design: Randomised controlled trial (therapy). Evidence level: 2- Country: France
Inclusion criteria: Women with histologically proven metastatic breast cancer Age ≥ 18 years WHO status + 0-2 Life expectancy > 2 months Adequate haematological and other laboratory criteria (defined) Ability to self administer the QOL questionnaire Written informed consent
Exclusion criteria: Those with endocrine insensitive tumour (negative ER/PR staining, progression after endocrine therapy or rapidly progressing disease where endocrine therapy was not indicated) Women with a single metastasis curable by RT or surgery Previous chemotherapy for metastatic disease Pregnant or lactating Brain or leptomeningeal involvement Contraindication to anthracycline-containing therapy LVEF <50% Other serious illness, medical or psychiatric condition History of cancer (other than BCC skin or CIS cervix)
Population: Number of patients = 210. Age range 32 to 79 years. Median age = 57 years
Interventions: 1] AD arm (n=107): Doxorubicin (A) at 50 mg per m ² i.v. over 15 minutes followed 1 hour later by docetaxel (DOC) at 75 mg per m ² i.v. over 1 hour. 2] AP arm (n=103): Doxorubicin at 50 mg per m ² i.v. over 15 minutes followed 1 hour later by paclitaxel (PAC) at 175 mg per m ² i.v. over 3 hours. Both combination treatments were given every three weeks for 4 cycles followed by the same taxane as monotherapy for a further 4 cycles. Dose reductions (details given) were employed in the case of unavoidable treatment delays from toxicity. Any patient experiencing febrile neutropenia at low dosage levels, LVEF reduced by 15% or falling below 50% or anyone suffering from any grade 3 non-haematological toxicity was withdrawn from study. Treatment was stopped in cases of disease progression, unacceptable toxicity or patient withdrawal of consent.
Outcomes: Primary outcome: Global QOL (EORT QLQ-C30 items 29 and 30) at baseline and after 4 cycles. Secondary outcomes: Overall response rate (ORR): complete response (CR), partial response

(PR), stable disease, disease progression (PD), progression-free survival (PFS), toxicity, overall survival (OS), QOL sub-group analyses and assessment after 8 cycles and 1 year after the study entry.

Follow up:

Three weeks before the study began, baseline tests were undertaken including medical history and physical examination, blood and biochemical tests, CT of thorax, abdomen and pelvis, bone scintigraphy, ECG and LVEF measurement. Baseline measures of QOL were obtained by self administered questionnaire (EORT QLQ-C30) within a week before the first treatment cycle.

Follow-up included haematology, physical examination, QOL assessment and serum biochemistry before each cycle of chemotherapy. Response was evaluated after cycles 2, 4 and 8 using CT scan and bone scintigraphy.

Five patients in the AD arm and one patient in the AP arm were ineligible due to: prior chemotherapy for MBC (n=1), abnormal liver enzymes (n=2), abnormal platelet count (n=1), hormone sensitivity (n=1) and found to have ovarian cancer (n=1). These patients were included in the ITT analysis.

The study was discontinued in 40 women (AD=25 and AP=15) because of disease progression and in 46 women (AD=22 and AP=24) for toxicity.

Median follow-up was 50.2 months. During this period 160 deaths were reported.

Results:

378 cycles of AD and 374 cycles of AP were given with a median number of cycles of 8 (range: 1-8) in each group.

Primary outcome - QOL:

Compliance was over 80% with baseline and 1st assessment (after 4 cycles) but dropped to 50% by 8 cycles. There was no significant difference between study arms for baseline scores or at the 1st assessment. Global QOL scores did not vary across time significantly between study arms.

Secondary outcome - QOL:

Global QOL scores were not significantly different between study arms either after 8 cycles or after 1 years following study entry whether comparing median scores or examining relative or absolute variations. Only sub-scores for diarrhoea (worse for AD patients after 8 cycles, P=0.004) and fatigue (worse for AP patients after 4 cycles, P=0.048) varied between AD and AP but at cycle 8 only 60/116 patients on study returned questionnaires.

Efficacy at 50.2 months:

ORR for AD = 39.6%

ORR for AP = 41.8% (nsd)

Median PFS for AD = 8.7 months (95%CI: 8.1-9.3)

Median PFS for AP = 8.0 months (95%CI: 6.9-9.0) (nsd)

Median OS for AD = 21.4 months (95%CI: 15.3-27.5)

Median OS for AP = 27.3 months (95%CI: 22.7-31.8) (nsd)

Safety:

There were 3 deaths due to toxicity (AD=2). There were grade 3/4 events in 67.2% of the 752 cycles administered:

AD arm vs AP arm % cycles 1-4:

Anaemia = 8.4 vs 4.9

Thrombocytopenia = 4.7 vs 1.00
Leukopenia = 49.5 vs 26.2 (P=0.01)
Neutropenia = 50.5 vs 39.8 (P=0.02)
Febrile neutropenia = 48.6 vs 21.4 (P<0.0001)
Nausea = 4.7 vs 1.9
Vomiting = 4.7 vs 1.00
Mucositis = 4.7 vs 1.00
Oedema = 0.9 vs 1.00
Peripheral neuropathy = 0.9 vs 6.8 (P=0.03)
Asthenia = 8.4 vs 1.9 (P=0.03)

AD arm vs AP arm % cycles 5-8:

Anaemia = 0 vs 1.3
Leukopenia = 12.5 vs 3.9
Neutropenia = 27.8 vs 7.8 (P<0.001)
Febrile neutropenia = 2.8 vs 1.3
Mucositis = 0 vs 1.3
Oedema = 2.8 vs 0
Peripheral neuropathy = 0 vs 7.8 (P=0.03)
Cardiopathy = 0 vs 2.6
Asthenia = 5.6 vs 6.5

General comments:

This paper describes the findings from a RCT comparing anthracycline (doxorubicin) combined with either taxane i.e. DOX+PAC vs DOX+DOC followed by four cycles of the same taxane as monotherapy. Women were recruited at ten French institutions between March 2000 and April 2004.

There is a strong possibility of selection bias in the self administered QOL questionnaires since those patients experiencing severe adverse events may have been more likely not to comply and hence their data is missing. Also, the authors stated that the '1-4 cycles' data were collected from people who had completed 5 cycles which therefore meant that 24 patients who had completed four cycles but progressed by the fifth cycle were omitted.

The authors were of the opinion that QOL assessments in large trials of first line therapy may not be appropriate and fail to offer additional useful information over and above standard efficacy outcomes. This may often be due to missing data. The conclusion was that the taxanes are of equal efficacy as first line therapy combined with anthracycline but with different toxicity profiles which nonetheless was not reflected by any obvious differences in QOL outcomes.

Despite being an apparently thorough trial there are few details of methodology with regard to allocation or randomisation (block method at a central agency) and it is not stated by whom the follow-up assessments were made or QOL questionnaires scored. The element of bias cannot be excluded and the results must therefore be viewed accordingly.

Health Economic Summary

A cost-utility analysis of chemotherapy sequences for the treatment of patients with advanced breast cancer

INTRODUCTION

Since metastatic breast cancer is incurable, the quality of patient's lives during the final stages of life with various forms of active chemotherapy and supportive and palliative care is of great

importance. However the economic cost of this treatment and care to the NHS must be considered and balanced.

NICE has previously issued guidance on the use of the taxanes, capecitabine and vinorelbine for use in the treatment of patients with advanced breast cancer in the form of three technology appraisals (TA30 (2001); TA54 (2002); TA62 (2003)). These appraisals are now being updated within the guideline for the treatment of advanced breast cancer. In light of new clinical evidence it is important that the economics of these chemotherapy agents are re-examined. In addition, the sequencing of these agents has not been considered in the economic literature to date and the neglect of sequential therapy as a comparator to combination therapies in previous technology appraisals was a concern to both the Appraisal Committee of the recent Gemcitabine STA (TA 116) and to the Advanced Breast Cancer Guideline Development Group.

EXISTING ECONOMIC EVIDENCE

There are a number of good quality economic evaluations investigating the cost-effectiveness of first and second-line chemotherapy regimes in patients with metastatic breast cancer, most of which were appraised for the original technology appraisals (summarised below). Four new full economic evaluations have been published since the review undertaken for the appraisals (Verma et al, 2005; Cooper et al, 2003; Verma & Ilersich, 2003; Li et al 2001). One partial economic evaluation considering the costs of third-line chemotherapy was published in 1999 but was not included in the previous reviews since third-line therapy was not part of the inclusion criteria. The main limitations of these studies are that none compare more than three types of therapy, nor do they consider more than one line of therapy. This highlights the need for de novo economic modelling to directly answer the review question.

TA30 – Taxanes

In the original appraisal no economic evaluations for the first line treatment¹ of breast cancer with a taxane were identified. For second-line treatment², seven economic evaluations were identified and reviewed. One compared paclitaxel with mitomycin but was submitted in confidence to NICE and therefore was not published in the subsequent HTA report. The other six compared paclitaxel and docetaxel in cost-utility analyses where the range of incremental QALYs gained was £1990-£2431³. In addition three analyses compared docetaxel and vinorelbine - one of which was carried out in the UK and yielded a cost-utility ratio for incremental QALYs gained was £14,050. The original guidance did not give any indication as to which taxane was preferred for second-line treatment of breast cancer, despite the evidence showing that docetaxel has a highly favourable cost-effectiveness ratio compared with paclitaxel.

TA54 – Vinorelbine

Evidence at the time of TA54 was scarce. The evidence reviewed for the appraisal showed no clinical benefit of vinorelbine monotherapy over other therapies as first-line treatment. Vinorelbine monotherapy as second-line treatment was slightly less effective than taxane therapy but was much less toxic. For a sub-group of patients (e.g. elderly) this was considered a useful treatment option and was backed up by economic evidence. None of the RCT data favoured vinorelbine combinations and the case-series data did not provide a robust alternative interpretation. The economics involved in the original appraisal comprised of two literature reviews (one investigated the use of vinorelbine as a single agent and the other investigated vinorelbine in combination with

¹ It is important to note that the term 'first-line treatment' is used here to describe treatment given to patients who are not anthracycline-resistant or failing. Since the number of patients in this category is now very small, the term 'first-line treatment' in the rest of this report refers to the first therapy received by a patient with advanced disease for which anthracycline therapy is not suitable.

² Similarly, 'second-line treatment' as referred to here is later referred to as 'first-line treatment' in the rest of this appendix.

³ The accepted threshold for evaluating the cost-effectiveness of any given treatment in the context of the UK is around £20,000-£30,000 per QALY. As such the range of £1,990-£2,431 per QALY shows docetaxel therapy to be very cost-effective compared to paclitaxel therapy.

other agents), with no independent modelling. The reviews found no economic evaluations investigating vinorelbine as combination therapy, and identified four economic analyses for vinorelbine monotherapy (Brown et al, 2001; Silberman et al, 1999; Launois et al, 1996; Leung et al, 1999), though one of these was in abstract form and therefore provided little detail. Three of these were fairly well conducted cost-effectiveness or cost-utility analyses, one of which was carried out in a UK setting from an NHS perspective (the remaining three were undertaken in Canada, the US and France). However they gave conflicting results, "when comparing the cost-effectiveness of vinorelbine, paclitaxel and docetaxel, one economic evaluation reported that vinorelbine was more effective and less costly than taxane therapy, one found vinorelbine to be less effective and less expensive than either of the taxanes and a third evaluation found vinorelbine to be less effective and more expensive than taxane therapy" (Lewis et al, 2002). In addition none of the studies adequately addressed the uncertainty surrounding their results.

TA 62 - Capecitabine

The only economic evidence available at the time of the appraisal was one abstract (not reviewed) and the economic model submitted by the manufacturer for both capecitabine monotherapy and in combination with docetaxel. Neither of these models has since been published in a peer-reviewed journal.

OBJECTIVES

This economic evaluation will assess the cost-effectiveness of several sequences of the main chemotherapy regimes (listed below), as well as supportive and palliative care, that are used to treat metastatic breast cancer patients who have received prior anthracycline therapy.

A secondary objective is to rule out certain strategies (i.e. sequences of therapy) that are likely not to be cost-effective from an NHS perspective.

To facilitate the economic analysis, an indirect treatment comparison will be carried out on RCTs for first-line treatment.

METHODS

Study Population

In contrast to the populations considered in the technology appraisals, the population of interest in this study is patients with metastatic breast cancer who have previously received anthracycline treatment which may have been given as adjuvant treatment. Aggressive treatment of early stage breast cancer has led to the presentation of such patients becoming the 'norm', and increasingly patients are even presenting with advanced disease that is resistant to or has failed taxane and anthracycline therapy (Jones et al, 2001).

Whilst no explicit distinction is made, it is assumed patients in whom the disease is hormone responsive will receive alternative/additional treatment. The clinical and economic evidence for the management of these patients is explored elsewhere in the guideline.

Interventions

First-line therapy options (T1):

Capecitabine + docetaxel combination therapy ('T1: CAP + DOC')

Gemcitabine + docetaxel combination therapy ('T1: DOC + GEM')

Paclitaxel monotherapy ('T1: PAC')
 Docetaxel monotherapy ('T1: DOC')

Second-line therapy options (T2):

Capecitabine monotherapy ('T2: CAP')
 Vinorelbine monotherapy ('T2: VIN')
 Supportive and Palliative Care only ('T2: No Chemo')

Third-line therapy options (T3):

Capecitabine monotherapy ('T3: CAP')
 Vinorelbine monotherapy ('T3: VIN')
 Supportive and Palliative Care only ('T3: No Chemo')

Table 1: Standard dosages assumed by the model

	<i>Dosage 1</i>	<i>Dosage 2</i>
Capecitabine + docetaxel	1250mg/m ² twice daily on days 1 - 14	75 mg/m ² on day 1
Gemcitabine + docetaxel	1250mg/m ² on days 1 and 8	75 mg/m ² on day 1
Paclitaxel monotherapy	175 mg/m ² on day 1	-
Docetaxel monotherapy	100 mg/m ² on day 1	-
Capecitabine monotherapy	1250mg/m ² twice daily on days 1 - 14	-
Vinorelbine monotherapy	30 mg/m ² , days 1 and 8	-

Structure of the Model

A decision tree was constructed to represent all the possible consequences resulting from a sequence of treatment. A total of 724 branches were estimated for seventeen different sequences of chemotherapy, listed below in table 2. It was assumed that a chemotherapy agent could not be used twice in the same sequence.

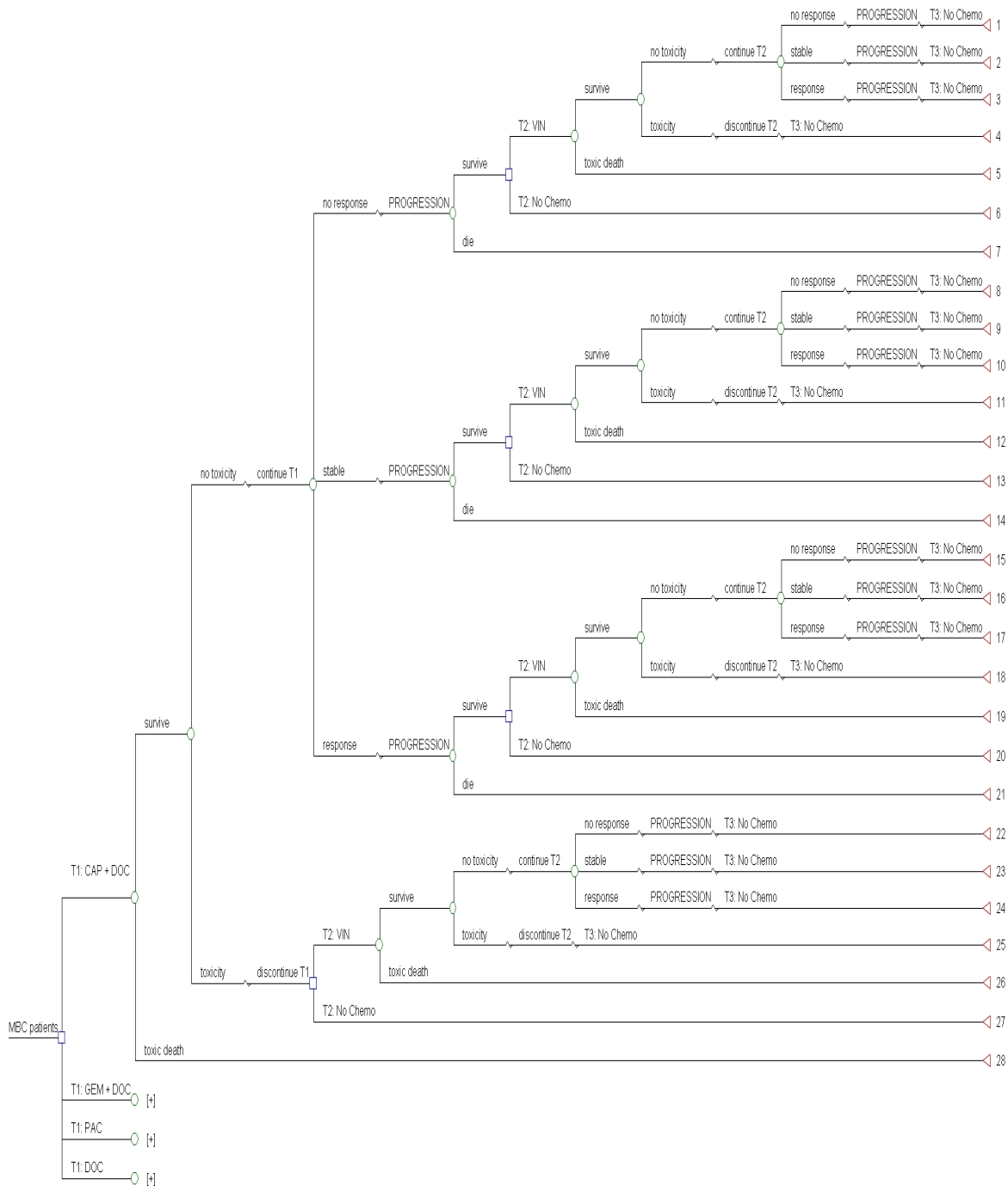
Table 2: The seventeen strategies considered in the model

Strategy	First-line (T1)	Second-line (T2)	Third-line (T3)
1	DOC+CAP	VIN	No Chemo
2	DOC+CAP	No Chemo	
3	GEM+DOC	CAP	VIN
4	GEM+DOC	CAP	No Chemo
5	GEM+DOC	VIN	CAP
6	GEM+DOC	VIN	No Chemo
7	GEM+DOC	No Chemo	
8	PAC (3-weekly)	CAP	VIN
9	PAC (3-weekly)	CAP	No Chemo
10	PAC (3-weekly)	VIN	CAP
11	PAC (3-weekly)	VIN	No Chemo

Draft for consultation

12	PAC (3-weekly)	No Chemo	
13	DOC	CAP	VIN
14	DOC	CAP	No Chemo
15	DOC	VIN	CAP
16	DOC	VIN	No Chemo
17	DOC	No Chemo	

Figure 1: decision tree (for first 28 branches)



The model begins by considering patients with metastatic breast cancer (who have received prior anthracycline therapy). The first decision is which first-line treatment to offer the patient. The decision tree shows explicitly all the possible decisions that could be taken (given the confines of our decision problem) and all the possible consequences resulting from this first decision (again we have limited these). Four first-line treatments are considered. Time is not made explicit in a decision tree model, but we assume the patient receives one cycle of the first line therapy. At this point, there is a possibility that the patient might die of a toxic death. If the patient dies of a toxic

death, that is the end of the possible outcomes associated with the treatment. It has been assumed that a toxic death can only occur after the first cycle of therapy.

If that patient survives the risk of toxic death, (s) he will then receive two more cycles of therapy. This brings the total number of cycles of therapy the patient has received at this point to three. The patient then faces another chance event of experiencing toxicity that will lead to the discontinuation of the current first-line treatment (no chance or decision to be taken here, this necessarily follows on from experiencing major toxicity). At this point we face another decision node, the choice of which second-line treatment to take. There is a time-lag of 1 month between discontinuing first-line therapy and starting on second-line therapy. If the patient didn't experience toxicity, (s) he will continue on first-line therapy. At this point it is assumed that response can be assessed, so the patient faces a probability of responding to therapy, of having stable disease or not.

For the purposes of the model, response is defined as complete or partial tumour response to the first-line therapy. Responders and stable patients go on to receive additional cycles of treatment, receiving in total the median number of cycles as reported in the RCTs investigating that therapy (in the case of all the interventions in the model, this was six cycles). Non-response is defined as patients who are classified as having progressive disease or their tumour was non-assessable. These patients do not receive further treatment. Regardless of whether the patient has responded to first-line treatment or not, progression is an inevitable outcome. However the time to progression will be different. Once the patient is experiencing progressive disease, (s) he faces the probability of dying from progressive disease. Indeed death only results from progressive disease or toxicity; the possibility of death from other causes was not considered to be relevant to the model due to the poor prognosis of these patients. This approach is consistent with other published economic evaluations. If the patient survives, (s) he will continue to second-line treatment.

At this decision node, there may be two or three possible second-line therapies. This is because it has been assumed that if capecitabine has been used as first-line treatment, or a part of a combination therapy given as first-line treatment (e.g. capecitabine + docetaxel), then it cannot be considered as a second-line therapy option. This is the scenario depicted in figure 1 above.

The patient then experiences the same chance events as with first-line treatment (chance of toxic death, chance of experiencing toxicity leading to discontinuation, chance of responding to second-line therapy). Once second-line therapy is discontinued or progression has been reached after completing the full course of second-line treatment, the patient continues onto third-line therapy. In Figure 1 this decision has only one possible option thus is not depicted with a decision node. Since both capecitabine and vinorelbine have been used by this point, the only treatment option left for this patient is Supportive and Palliative Care ('No Chemotherapy'). There is only one possible outcome from the 'No Chemotherapy' option, so this branch terminates. If third-line treatment is a chemotherapy regime, the same chance events as with first-line and second-line treatment may occur (the chance of toxic death, chance of experiencing toxicity leading to discontinuation, chance of responding to second-line therapy).

Clinical Evidence

First-Line Treatment – An indirect treatment comparison

An RCT or a meta-analysis of RCTs comparing all the interventions of interest to this analysis is not available. Indeed using conventional techniques this would not be possible due to the different comparisons made by each trial. It is common for new therapies to be introduced into clinical practice before formal treatment comparisons with the current standard approach or other new agents have been planned or carried out.

Using just one arm of one RCT to give us information on each intervention would cause a number of methodological problems. Not only would this not make use of all the available evidence, it would also lose the effect of randomization which is what gives the RCT its gold standard.

In the absence of direct comparative evidence, an indirect treatment comparison has been performed to inform the parameters of the economic model and ultimately ensure the recommendations in the guideline are based on all available evidence. Indirect comparisons use evidence from A vs. B and A vs. C trials to draw conclusions about the effect of B relative to C. The main assumption made using this approach to evidence synthesis is that the evidence is consistent. That is, the treatment effect of B relative to C estimated by a real trial comparing B vs. C would be the same as the treatment effect estimated by the A vs. B and A vs. C trials if they had included C and B arms respectively. This assumption is also implicit in cost-effectiveness analysis, since evidence is routinely combined from a variety of sources, thus consistency has to be assumed.

The clinical evidence review for the update of each technology appraisal was performed separately, which informed the search strategy for these topics. As such a full systematic search for all treatments for metastatic breast cancer was not undertaken. The network of RCT evidence is thus made up of trials that were identified for the original appraisals, from the individual update searches for the three technology appraisals and from an unsystematic manual search aiming to identify trials that may have been excluded from the clinical review (due to stricter inclusion criteria). Randomised controlled trials that involved one or more of the interventions of interest were included in the network of evidence. Whilst the economic model assesses three lines of therapy, no RCTs were identified for second- or third-line therapy. Thus, the indirect treatment comparison was only carried out on first-line treatment options.

The indirect comparison was undertaken using two separate statistical models using the statistical computer software, WinBUGS. The first describes the relationship between toxic deaths and discontinuation due to toxicity, whilst the second links the response rate, progression rates and mortality. The networks of RCT evidence for each statistical model are depicted below (figures 2 and 3); each line represents one RCT and the shading of certain interventions highlights those that are of interest in our decision problem. Other interventions are included to add to the information we can obtain on the interventions that are of interest, through indirect comparisons. The evidence structure is presented below the diagram in table 3. If all the trials reported all the data that was needed, all trials would have been included in both the indirect treatment comparisons. Since there were gaps in the data, three of the trials (Sjostrom 1998, Bonneterre 2002 and Monnier 1998) were excluded from the analysis of progression and survival. Whilst the analysis was undertaken from a Bayesian framework, flat priors were used in both statistical models and thus did not impact on the results.

Figure 2: RCT network for toxicity model

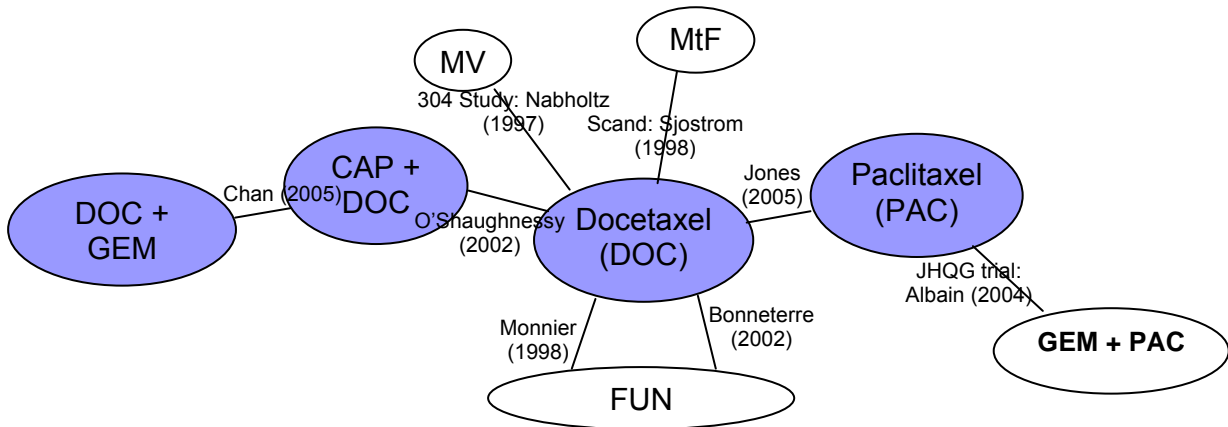


Figure 3: RCT network for survival model

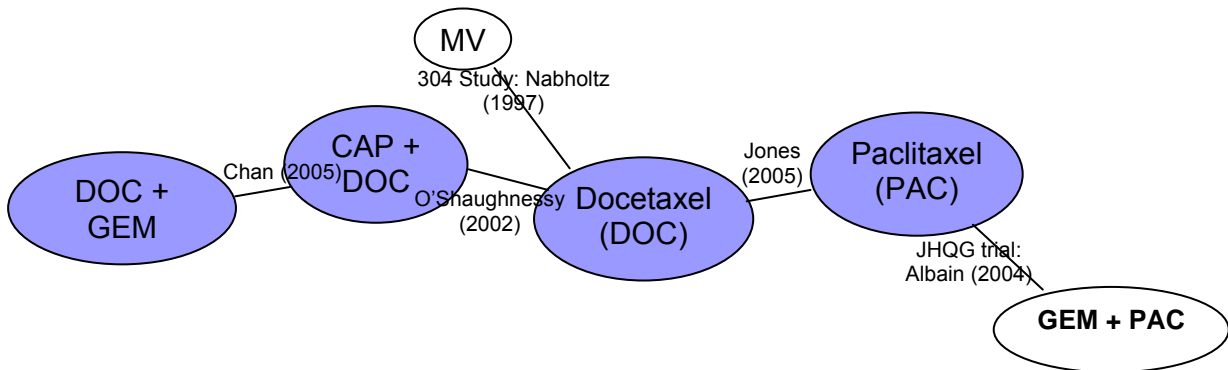


Table 3: evidence structure

Study	Number of toxic deaths	Number discontinuing due to toxicity	Number of responders	Duration of response (for responders)	Median time to progression (for all)	Median overall survival (for all)	Log hazard ratio
Jones 2005	✓	✓	✓	✓			✓
O'Shaughnessy 2002	✓	✓	✓	✓	✓	✓	
Albain 2004	✓	✓	✓	✓	✓	✓	
Chan 2005	✓	✓	✓	✓	✓		
Nabholtz 1997	✓	✓	✓		✓	✓	
Sjostrom 1998		✓					
Bonneterre 2002	✓						
Monnier 1998	✓						

The text that follows is a simple description of the methods used for the indirect treatment comparisons. The WinBUGS code is not presented here but is available from the author on request (please contact nicky.welton@bristol.ac.uk).

Toxicity model

A number of assumptions were made in order to get the most out of the data. Firstly, it was assumed that the toxic death rate did not vary by study, so a fixed effects model was used. Secondly, the two measures of toxicity (toxic death and discontinuation due to toxicity) are related by a constant, beta, which was allowed to vary by study (from a random effects model). Thirdly the baseline probability of toxic death (to which all the relative effects are compared, in this case the probability of toxic death for docetaxel) was estimated by a random effects model of the arms of the three trials involving docetaxel.

Survival model

In line with the assumptions made in structuring the economic model, it is assumed that patients are categorised at 9 weeks as responders (r), stable (s), with progressive disease (pd), or non-assessable (na). There is data on the split between these groups from most studies, although one study only reports whether a responder, stable or not, and one study only reports whether a responder or not. It was assumed that the split between categories follow a multinomial distribution:

$$(n_r, n_s, n_{pd}, n_{na}) \sim \text{Multinomial}((p_r, p_s, p_{pd}, p_{na}), N)$$

We model the effect of treatment using multinomial logistic regression. Let

$$q_{i,1} = p(\text{responder}) = p_{i,r}$$

$$q_{i,2} = p(\text{stable} \mid \text{non-responder}) = p_{i,s} / (1 - p_{i,r})$$

$$q_{i,3} = p(\text{prog.disease} \mid \text{non-responder, non-stable}) = p_{i,pd} / (1 - p_{i,r} - p_{i,s})$$

$$p_{na} = 1 - p_r - p_s - p_{pd}$$

We assume the following model for the conditional probabilities, q :

$$\text{logit}(q_{i,1}) = \varphi_{s(i)} + (\theta_{t(i),1} - \theta_{b(i),1})$$

$$\text{logit}(q_{i,2}) = \varphi_{s(i)} + \zeta_{s(i)} + (\theta_{t(i),2} - \theta_{b(i),2}); \quad \zeta_j \sim N(m_\zeta, sd_\zeta^2)$$

$$\text{logit}(q_{i,3}) = \varphi_{s(i)} + \gamma_{s(i)} + (\theta_{t(i),3} - \theta_{b(i),3}); \quad \gamma_j \sim N(m_\gamma, sd_\gamma^2)$$

Key assumptions:

- Fixed treatment effects which differ for different conditional outcomes: responders; stable|non-responder; and prog.disease|{non-responder & non-stable}.
- The proportion of responders depends on study.
- The baseline log-odds of the conditional outcomes stable|non-responder; and prog.disease|{non-responder & non-stable} differ from that for responders by study specific terms ζ_j and γ_j which come from random effects distributions.

Most studies reported median time to progression for responders and for all. We assume exponential distributions for the time to progression in responders and non-responders with rates λ_r and λ_{nr} respectively. We therefore needed a model for the progression rate for responders, λ_r , and non-responders, λ_{nr} . We put a log-linear model on the progression rate in responders and stable:

$$\log(\lambda_r) = \alpha_{s(i)} + (d_{t(i)} - d_{b(i)})$$

$$\log(\lambda_s) = \alpha_{s(i)} + \eta_{s(i)} + (d_{t(i)} - d_{b(i)}); \quad \eta_j \sim N(m_\eta, sd_\eta^2)$$

Key assumptions:

- Study specific baselines for responders
- Random effects model for log-hazard ratio for stable vs responder
- Fixed treatment effect across studies, which is the same for responders and stable individuals.

The mean progression time in non-responders is a weighted average of mean progression time for stable, non-assessable, and progressive disease patients, giving progression rate in non-responders of:

$$\lambda_{nr} = \frac{1}{\left(\frac{(p_{na} + p_s)}{\lambda_s(1 - p_r)} + \frac{1.5 p_{pd}}{(1 - p_r)} \right)}$$

Key assumptions:

- Time to progression is 4.5 weeks (1.125 months) for those with progressive disease.
- Non-assessable patients have the same progression rate as progressive patients.

Most studies reported median time to mortality for all patients. If we assume a constant term linking progression rates with mortality rates, then we can model mortality in exactly the same way as for progression. However, we do not know the mortality rate ($1/\mu$) for those with progressive disease, and so this was estimated from the data.

We assume exponential distributions for the time to mortality in responders and non-responders with rates μ_r and μ_{nr} respectively. We therefore need a model for the mortality rate for responders, μ_r , and non-responders, μ_{nr} . We put a log-linear model on the mortality rate in responders and stable, which differ from log progression rates by a constant, which depends on study, but assumed to come from a random effects distribution:

$$\log(\mu_r) = \log(\lambda_r) + \beta_{s(i)}; \quad \beta_j \sim N(m_\beta, sd_\beta^2)$$

$$\log(\mu_s) = \log(\lambda_s) + \beta_{s(i)}$$

The mean survival time in non-responders is a weighted average of mean survival time for stable, non-assessable, and progressive disease patients, giving mortality rate in non-responders of:

$$\mu_{nr} = \frac{1}{\left(\frac{(p_{na} + p_s)}{\mu_s(1 - p_r)} + \frac{\kappa p_{pd}}{(1 - p_r)} \right)}$$

Key assumptions:

- Random effects model on the log-hazard ratio's (β_j) of mortality relative to progression
- Fixed mean survival time λ for those with progressive disease.
- Non-assessable patients have the same mortality rate as progressive patients.

Second-line Treatment

There is one randomised controlled trial and seven non-randomised studies investigating second-line therapy. No evidence was found to report the effectiveness of the 'No chemotherapy' intervention.

The Martin et al (2007) RCT was used to provide data on vinorelbine monotherapy as second-line treatment by agreement with the GDG since the trial has a mixed patient population (patients received vinorelbine as first-, second- and third- line treatment). Although there were two other observational studies investigating vinorelbine monotherapy (Zelek 2001; Udom 2000) they were both small trials and the Martin RCT was considered by the GDG subgroup to provide the best estimate of vinorelbine monotherapy in the second-line setting.

Five non-randomised studies were identified for capecitabine monotherapy as second-line treatment (Fumoleau et al. 2004; Lee et al. 2004; Pierga et al. 2004; Reichardt et al. 2003; Wist et al. 2004). Whilst all were considered acceptable in terms of being able to provide reasonably robust evidence, not all trials provided data on the same parameters. Pierga et al 2004 provided data on response duration, duration of stable disease and time to progression for all. As such this trial was used to provide information for the model on capecitabine monotherapy as second-line treatment.

No evidence was found to report the effectiveness of the 'No chemotherapy' intervention. It was assumed that 'No Chemotherapy' would result in no progression-free survival and 5 months survival with progressive disease.

Third-line treatment

No evidence for capecitabine or vinorelbine monotherapy as third-line treatment was identified. It was therefore assumed that the same data for second-line treatment would provide a suitable estimate of third-line treatment, since the patient populations included some patients receiving the study therapy as third-line. In the base-case analysis, no adjustments to the data were made although the effect of reducing the survival estimates by varying degrees will be explored in the sensitivity analysis.

Health Benefits

Probabilities

The probabilities of toxic death and of discontinuing treatment due to toxicity shown in table 4 were all estimated via the ITC statistical model. The toxicity data for second and third-line treatment are shown in table 5.

Table 4: probabilities estimated by the indirect treatment comparison

Intervention	Toxic death rate	Discontinuation due to toxicity
T1:DOC+CAP	0.020	0.337
T1:GEM+DOC	0.008	0.201
T1:PAC	0.003	0.116
T1: DOC	0.014	0.278

Table 5: probabilities for second and third-line treatment

Intervention	Source	Toxic death	Discontinuation
--------------	--------	-------------	-----------------

		rate	due to toxicity
T2 and T3: VIN	Martin et al, 2007	0.008	0.048
T2 and T3: CAP	Pierga et al, 2004	0.000	0.162

The probabilities of response, stabilisation of disease, disease progression and non-assessability were estimated via the second ITC statistical model, shown in table 6 below:

Table 6: probabilities estimated by the indirect treatment comparison

Intervention	Response	Stable	Progression	Non-assessable
T1:DOC+CAP	0.4070	0.3427	0.1244	0.1258
T1:GEM+DOC	0.4023	0.4209	0.1148	0.0620
T1:PAC	0.2316	0.3911	0.3234	0.0539
T1: DOC	0.2899	0.3841	0.2200	0.1060

For the economic model, it was assumed that non-assessable patients were the same as patients with progressive disease.

Table 7: probabilities for second and third-line treatment

Intervention	Source	Response	Stable	Non-response
T2 and T3: VIN	Martin et al 2007	0.262	0.254	0.484
T2 and T3: CAP	Pierga et al 2004	0.152	0.335	0.513

Survival

Overall survival (OS) was assumed to be the sum of time to progression (TTP_{t1}) of first-line treatment, TTP from second-line treatment (TTP_{t2}), TTP from third-line treatment (TTP_{t3}) and the period from progression to death (assumed to be 5 months). This assumption implies that chemotherapy impacts on time to progression, and through that overall survival. However the time from (final) progression to death is fixed regardless of prior treatment.

Mean 'progression-free' survival times (in months) were estimated from the statistical model on survival and are reported below in table 8. It is assumed that time to progression for patients with progressive disease reported as their best response to treatment (or if the tumour was not assessable) is 1.125 months (4.5 weeks).

Table 8: Survival data estimated by the indirect treatment comparison (in months)

Intervention	TTP - Responders mean	TTP - Stable mean
T1:DOC+CAP	12.19	7.53
T1:GEM+DOC	11.08	6.84
T1:PAC	5.63	3.47
T1: DOC	10.27	6.34

Mean values are used for the economic evaluation since they are a more appropriate measure of the average at a population level. Since only median values were reported in the Martin 2007 and Pierga 2004 trials, it was assumed that survival and time to progression followed exponential distributions. Median values were then converted to mean values by calculating the baseline hazard:

$$h = -\ln(0.5)/t_{\text{med}}$$

$$t_{\text{mean}} = 1/h.$$

where, h =baseline absolute hazard; t_{med} =median survival time; t_{mean} =mean survival time

Table 9: Survival data for second and third-line treatment (in months)

Intervention	Source	TTP - Responders	TTP - Stable	TTP - Progression
T2 and T3: VIN	Martin et al 2007	5.77	5.77	1.13
T2 and T3: CAP	Pierga et al 2003	12.84	9.52	3.45

Utilities

Utility weights were linked to the time spent at different points of the pathway (not strictly health states since we did not use a Markov process) to calculate QALYs. No trials reported utility losses due to toxicity or to progressive disease, so the proportion of patients in each arm of an RCT that progressed or discontinued treatment due to toxicity were relevant published utility weights to estimate the overall utility. There are a number of studies that report utility weights in the treatment of advanced breast cancer. The most recent pooling of utilities from different sources (all derived from oncology nurses using the Standard Gamble technique) was published by Cooper and co-workers (2003). A number of assumptions had to be made about the utility associated with time spent between treatment (we assume utility with progressive disease, 0.45); the time spent on treatment before response could be assessed (we assume utility associated with stable disease, 0.65, to ensure consistency with the indirect treatment comparison since at this stage by definition the disease is not yet progressive); and time before toxicities identified after 3 cycles of treatment (we assume utility associated with progressive disease, 0.45).

Table 10: utility values from Cooper et al (2003)

Health state	Pooled utilities
Response	0.81
Stable disease	0.65
Stable disease and febrile neutropenia or infection with hospitalisation	0.44
Progressive disease	0.45
Progressive disease with toxicity (assumption)	0.35
Death	0

Cost Estimation

The costs considered in this analysis are only those relevant to the UK NHS, in accordance with the perspective taken by the NICE Reference Case for economic evaluations. Costs were estimated in 2006-7 prices. Where costs have been taken from sources using a different price year, they have been inflated using the Hospital and Community Health Services Pay and Prices Index (PSSRU, 2007).

There are broadly five categories of costs considered in the model:

- Cost of treatment
- Cost of assessment/ follow-up
- Cost of treating adverse events
- Cost of supportive and palliative care
- Costs associated with death

Cost of treatment

The average dose for each regime was presented in table 1. The possibility of reducing the dose (in response to an adverse event) was not allowed for in the model. The drug acquisition cost per cycle were calculated for each chemotherapy regime based on an average dose per patient (standard 1.75m²), the average number of doses per cycle and the average list price per mg.

Whilst it is recognised that discounts are available on some of these drugs, the list price was used in the base case as recommended in the NICE Reference Case. The effect of these drug discounts will be explored in the sensitivity analysis. Where the price is given for both the generic and proprietary drug, the cheapest is used in the base-case.

Table 11: Drug acquisition costs (1)

Drug	Vinorelbine		Paclitaxel		Docetaxel	
Brand name	(generic)	Navelbine	(generic)	Taxol	Taxotere	
Manufacturer	n/a	Fabre	n/a	Bristol-Myers Squibb	Sanofi-Aventis	
List prices, £ (BNF 54, Sept 2007):						
0 ml vial					162.75	
1 ml vial	32.95	29.75				
2 ml vial					534.75	
5 ml vial	153.98	139.98	111.41	116.05		
16.7 ml vial			333.91	347.82		
25 ml vial			500.86	521.73		
50 ml vial			1001.72	1043.46		
i.v. concentrate (mg/ml)	10	10	6	6	40	
Dose (mg/m ²)	30	30	175	175	100	75
Average dose	52.5	52.5	306.25	306.25	175	131.25
Average cost per mg (£)	3.12	2.83	3.36	3.50	6.98	6.98
Average drug cost per dose (£)	163.56	148.51	1028.17	1071.01	1220.63	915.47
Premedication cost per dose (£)					2.56	2.56
Number of doses per cycle	2	2	1	1	1	1
Average drug cost per cycle (£)	327.13	297.03	1028.17	1071.01	1223.18	918.02

Table 12: Drug acquisition costs (2)

Orally administered		Injection (powder)	
Drug	Capecitabine	Drug	Gemcitabine
Brand name	Xeloda	Brand name	Gemzar
Manufacturer	Roche	Manufacturer	Eli Lilly
Dose (mg/m²)	1250	200mg vial	32.55
Dose per administration	2150	1g vial	162.76
150mg tablets required	1	Average cost per mg	0.16
500mg tablets required	4	Dose (mg/m²)	1250
Cost per 150mg pack (60 tab)	44.47	Average dose	2187.5
Cost per 150mg tablet	0.741166667	Average cost per dose	356.03
Cost per 500mg pack (120 tab)	295.06		
Cost per 500mg tablet	2.458833333	Number of doses per cycle	2
Cost per administration	10.5765		

No of doses per cycle	28		
Average drug cost per cycle	296.142	Average drug cost per cycle	712.0677083

In addition to the drug acquisition costs, the cost of administering the drug was estimated from the NHS National Reference Costs. For therapies administered by i.v. or injection (gemcitabine), the cost used was £293 for outpatient delivery of complex perenteral chemotherapy and subsequent elements. This cost includes hospital overheads, the administration costs of chemotherapy and clinical time, but does not, for example, distinguish between different i.v. infusion times of paclitaxel vs. docetaxel. For drugs administered orally (capecitabine) the administration costs were estimated using the outpatient tariff, £209 for first attendance and then £82 for subsequent attendances. It has been assumed that one outpatient appointment would be required per cycle of therapy (one every three weeks). In the case of combination therapy it has been assumed that two drugs can be administered at one time, thus requiring the cost of only one administration to be considered. In addition to the drug acquisition and drug administration costs, it has been assumed that a consultation with an oncologist (£209 for first attendance, National Reference Costs 2006-7) would be necessary at the starting cycle.

Cost of assessment/ follow-up

The cost of taking one CT scan (2 areas, with contrast) every three cycles of treatment was used as a proxy for the cost of assessing response (NHS Reference Costs, 2006-7). This is equivalent to £125 for non-responders, £250 for responders. This is an attempt to capture the continuous nature of assessing response.

Once the patient has finished chemotherapy and achieves a response there will still be a cost associated with the contact the patient receives from her consultant. (The cost of contact with other health professionals is included in supportive care package 1 below). Cost of one consultation with specialist every 2 months after treatment has finished (£105 per month, NHS Reference costs 2006-7) is used as a proxy for follow-up costs.

Response is not assessed when first-line chemotherapy ends so the cost of one CT scan is included before the patient begins the next line of chemotherapy.

Cost of treating adverse events

The cost of treating major toxicities (which necessarily lead to the discontinuation of treatment) was estimated as £804, the mean of two costs from the literature; from the cost of treating severe infection or febrile neutropenia in hospital £1,281 (Cooper et al, 2003) and the cost of treating a severe infection or febrile neutropenia at home £328 (Cooper et al, 2003), both reported here already inflated to 2006-7 prices. This cost was used across all treatments, so was not specific to the type of toxicity that leads to discontinuation which we know does vary by therapy.

Cost of supportive and palliative care

Due to the nature of supportive and palliative, three likely 'packages' of care are described below for patients at different points along the care pathway.

o Package 1

The first package of care describes an average level of supportive care a patient receiving chemotherapy might be expected to receive from the time of first cycle of treatment until the onset of progressive disease at which point the next line of chemotherapy is started. Given the model structure, this package of care is given to a patient until they begin the 'no chemotherapy' option. For some strategies this package of care will be given for the whole time spent in the model.

Time-related elements:

Community nurse: home visit 20m, £24.00, 1 per fortnight (PSSRU, 2007)

GP contact: 1 surgery visit £34.00 every month (PSSRU, 2007)

Clinical nurse specialist 1hr contact time, £74.00, 1 per month (PSSRU, 2007)

Time non-related elements:

Social worker: 1hr client-related work but not direct contact time, £34.00 (PSSRU, 2007)

○ **Package 2**

The second package of care describes an average level of supportive and palliative care a patient receiving the 'no chemotherapy' intervention might be expected to receive until the last two weeks of life. This package of care is also included for the patient that follows the strategies in the model with three lines of chemotherapy, from the time of progression until the two weeks before death. Unlike the care given in package 1, all elements of the care delivered in package 2 are time-related.

Time-related elements (weekly costs):

Community nurse: home visit 20m, £24.00, 1 per week (PSSRU, 2007)

Clinical nurse specialist: 1hr contact time, £74.00, 1 per week (PSSRU, 2007)

GP contact: 1 home visit, £27.50, every fortnight (PSSRU, 2007)

Therapist⁴: 1 hour, £20.00, every fortnight (PSSRU, 2007)

○ **Package 3**

The third package of supportive and palliative care is a cost for the more intensive needs of patients in the final two weeks of life. If this cost was attributable to all patients dying in the model, it would be superfluous to the analysis since we are interested solely in incremental costs and incremental benefits. This package of care is not however given to patients who die in the model from toxic death. Since the toxic death varies (albeit not greatly) between the interventions compared in the model, the cost of package 3 supportive and palliative care does need to be taken into account.

The cost used was a weighted average of the three costs reported in the Marie Curie commissioned report into the cost of dying at home (inflated as previously described to 2006/7 prices).

last 14 days - in hospital, £4,706

last 14 days - in Marie Curie hospice, £5,867

last 14 days - at home (with community support), £2,428

The weights applied to calculate this average were 40% deaths occurring in hospital, 10% occurring in a hospice and the remaining 50% of deaths occurring at home. The cost of the last two weeks of care was therefore estimated to be £3,418.

Costs associated with death

Apart from package 3 of supportive and palliative care, the other cost associated with death included in the model is the cost of toxic death. No costs related to toxic deaths were reported explicitly for any of the published economic evaluations, despite all papers considering the risk of toxic death. A proxy was used by way of the mean of two costs from the literature; from the cost of 7 days hospitalisation and treatment of severe febrile neutropenia £3,586 (Brown et al, 2001) and the cost of treating a severe infection in hospital £988 (Cooper et al 2003), both reported here already inflated to 2006-7 prices. In total the cost of toxic death used in the model is £2,287.

⁴ The type of therapist was not made explicit. The unit cost of all therapists listed in the PSSRU costs was £40 per hour. This was roughly the same for an hour of home visiting time.

Discounting

Discounting was not conducted, so the results that follow are the undiscounted costs and health outcomes. However we would not expect discounting to have much impact on the results of the model since many of the possible pathways through the model are associated with survival of less than 24 months. In addition the majority of the costs for pathways that do result in a longer survival, come at the beginning rather than spread evenly across the year.

TYPE OF ANALYSIS

A cost-utility analysis was performed given that the health outcome preferred by NICE is the QALY and quality of life is of particular importance to patients with metastatic cancer. An incremental cost-effectiveness analysis was conducted after ranking the alternative strategies from the most to the least cost-effective and excluding any dominated strategies (i.e. those strategies achieving lower effectiveness and incurring higher costs when compared to any other, *highlighted in table 14 in light grey*, or those which are ruled out if they achieve lower effectiveness and higher costs than a combination of two other strategies, *highlighted in table 14 in dark grey*).

SENSITIVITY ANALYSIS

A series of one-way deterministic sensitivity analyses were conducted to assess the robustness of the study results. 'One-way sensitivity analysis' describes the process of changing one parameter in the model and analysing the results of the model analysed to see if this parameter influences any of the overall results.

Five sources were thought to contribute most to the uncertainty surrounding the analysis; the utility values used in the analysis, the data used on the effectiveness of capecitabine monotherapy, the effectiveness of third-line therapy, possible price discounts and the calculation of overall survival. A number of scenarios were investigated as outlined below:

o Utility values

Although the most current utility values were used in the analysis (pooled by Cooper et al, 2003), the guideline development group were concerned about the validity of values ascribed to the different health states patients may experience. An arbitrary 10% increase and decrease in all the utility values used in the model was explored. The effect of just increasing the utility ascribed to progressive disease by 10% was tested. In addition the utility ascribed to patients with toxicity was varied from the base-case value of 0.44 to 0.35 (to equal the utility associated with progressive disease with toxicity).

o Effectiveness of capecitabine monotherapy

It was noted that the time to progression associated with capecitabine monotherapy was high. Therefore these estimates were reduced by one third in this scenario.

o Effectiveness of third-line treatment

No evidence was available for the effectiveness of third-line therapy, so both capecitabine and vinorelbine monotherapies were assumed to work as well as for second-line therapy. This was justified by the fact that the data used to inform the second-line therapy parameters in the model came from trials with mixed patient populations which included patients who were receiving the study therapy as third-line. The effect of reducing the response and disease stabilisation rates by one third, and separately reducing the time to progression estimates by one third was investigated.

o Price discounts

Price discounts are available across England and Wales on paclitaxel and vinorelbine since generic versions are available. However there is not one single agreed price discount available for either agent that is applicable across the whole of England and Wales. Therefore a number of different price discounts for paclitaxel were investigated (50%, 60%, 70%, 80%, 90%) as well as the effect of a price reduction also available for vinorelbine, vinorelbine 45% discount, paclitaxel 90% discount (current price discounts suggested by the Purchasing and Supply Agency database, eMIT).

○ **Calculation of overall survival**

Whilst it was acknowledged the calculation of overall survival was subject to uncertainty, this assumption was inherent to the structure of the model and was not tested in the sensitivity analysis. However the time from progression to death (assumed to be 5 months in the base-case analysis) was varied from 4 – 6 months.

However these scenarios are unlikely to happen independently; they are more likely to occur concurrently. A probabilistic sensitivity analysis, which allows multiple parameters to vary over specified distributions from which are then sampled at random many times, was not conducted but is planned to be undertaken during the consultation period for this guideline. This should provide a better picture of the uncertainty surrounding the analysis.

RESULTS

Base-case results

The base-case results are shown listed by strategy, in *table 13* below. There is a considerable difference between the strategies in terms of survival, quality of life and associated costs. The overall survival from each strategy ranges from just over 23 months (strategy 5: GEM+DOC, VIN, CAP) to just 8.5 months (strategy 12: PAC, No Chemo). Strategy 3 yields the highest number of QALYs (1.1896) compared to 0.3645 for strategy 12. Total costs for each strategy ranged from £14,000 (strategy 12) to over double that for strategy 3, £31,500.

Table 13: base-case results, by strategy

Strategy	First line	Second line	Third line	Total Expected Pyears	Total Expected LYs	Total Expected QALYs	Total Expected Costs
1	DOC+CAP	VIN	No Chemo	0.7833	1.2643	0.7694	£21,406
2	DOC+CAP	No Chemo		0.5009	0.9283	0.5452	£15,526
3	GEM+DOC	CAP	VIN	1.3392	1.9352	1.1896	£31,479
4	GEM+DOC	CAP	No Chemo	1.0600	1.5768	0.9734	£25,882
5	GEM+DOC	VIN	CAP	1.3422	1.9405	1.1857	£30,859
6	GEM+DOC	VIN	No Chemo	0.8306	1.3390	0.8230	£27,124
7	GEM+DOC	No Chemo		0.5443	0.9691	0.5827	£21,056
8	PAC	CAP	VIN	1.0532	1.6240	0.9739	£24,521
9	PAC	CAP	No Chemo	0.7716	1.2763	0.7527	£18,871
10	PAC	VIN	CAP	1.0551	1.6377	0.9642	£23,872
11	PAC	VIN	No Chemo	0.5411	1.0359	0.6009	£20,119
12	PAC	No Chemo		0.2534	0.6754	0.3645	£14,022
13	DOC	CAP	VIN	1.2043	1.7680	1.0738	£26,442
14	DOC	CAP	No Chemo	0.9197	1.4150	0.8500	£20,727
15	DOC	VIN	CAP	1.2002	1.7726	1.0592	£25,675
16	DOC	VIN	No Chemo	0.6916	1.1771	0.6997	£21,962
17	DOC	No Chemo		0.4069	0.8337	0.4718	£15,928

Pfyears = progression-free years, LYs = life years, QALYs = quality adjusted life years

Incremental cost-effectiveness analysis

Using QALYs as the outcome measure, an incremental cost-effectiveness analysis was performed by first ranking the strategies according to the cost per patient (highest to lowest). This allowed the dominated strategies to be identified and ruled out of the incremental analysis. Any strategies achieving fewer QALYs and incurring higher costs when compared to any other are ruled out by simple dominance (highlighted in *table 14* in light grey), and any strategies that achieve fewer QALYs and higher costs than a combination of two other strategies are ruled out via extended dominance (highlighted in *table 14* in dark grey). This left seven remaining strategies (2, 3, 5, 9, 12, 14 and 15) which are labelled in figure 3 below.

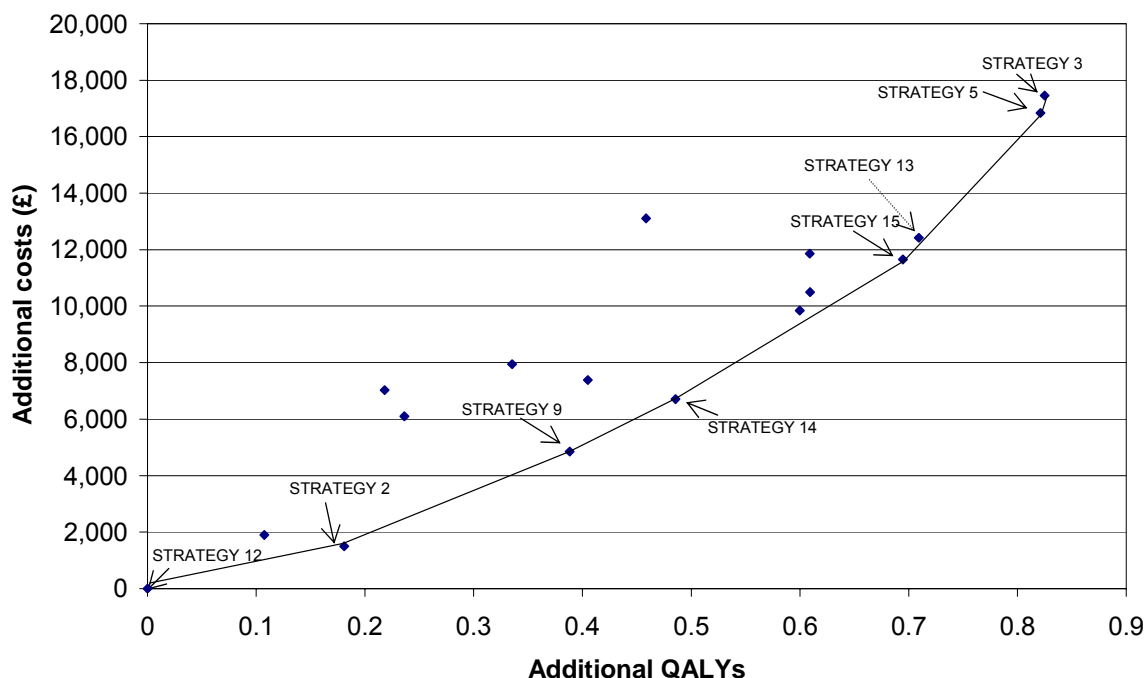
Table 14: incremental results

Strategy	T1	T2	T3	Total Expected QALYs	Total Expected Costs	ICERs
3	GEM+DOC	CAP	VIN	1.1896	£31,479	£160,748
5	GEM+DOC	VIN	CAP	1.1857	£30,859	£40,959
6	GEM+DOC	VIN	No Chemo	0.8230	£27,124	
13	DOC	CAP	VIN	1.0738	£26,442	
4	GEM+DOC	CAP	No Chemo	0.9734	£25,882	
15	DOC	VIN	CAP	1.0592	£25,675	£23,660

8	PAC	CAP	VIN	0.9739	£24,521	
10	PAC	VIN	CAP	0.9642	£23,872	
16	DOC	VIN	No Chemo	0.6997	£21,962	
1	DOC+CAP	VIN	No Chemo	0.7694	£21,406	
7	GEM+DOC	No Chemo		0.5827	£21,056	
14	DOC	CAP	No Chemo	0.8500	£20,727	£19,072
11	PAC	VIN	No Chemo	0.6009	£20,119	
9	PAC	CAP	No Chemo	0.7527	£18,871	£16,119
17	DOC	No Chemo		0.4718	£15,928	
2	DOC+CAP	No Chemo		0.5452	£15,526	£8,325
12	PAC	No Chemo		0.3645	£14,022	

PFyears = progression-free years, LYs = life years, QALYs = quality adjusted life years, ICERs = incremental cost-effectiveness ratios (see text below for explanation).

Figure 4: incremental cost-effectiveness



The seven unshaded strategies in *table 14* above (strategies 2, 3, 5, 6, 12, 14 and 15) are non-dominated strategies which were considered in the incremental analysis. All the other strategies are considered not to be cost-effective so would never be chosen on the basis of cost-effectiveness. The incremental cost-effectiveness ratios (ICERs) shown in the last column of *table 14* are the ratios of cost and health benefit for each strategy compared to the next best strategy. NICE recommends the use of a threshold of £20,000 per QALY. Using a threshold value of £20,000 per QALY, strategy 14 (docetaxel followed by capecitabine followed by no chemotherapy) was shown to be most cost-effective since it maximises health benefits given the budget constraint. However there may be compelling reasons to accept a slightly higher ICER of up to £30,000 per QALY which would make strategy 15 (docetaxel followed by vinorelbine and

then capecitabine) most cost-effective since it maximises QALYs below this threshold. Due to the multitude of strategies in the analysis, the results need careful interpretation. Since there is very little difference between strategies 13 (docetaxel followed by capecitabine followed by vinorelbine) and 15, in terms of QALYs, and given the uncertainty surrounding these point estimates, it is not clear which strategy is dominated and thus which should be excluded from the incremental analysis.

Strategies 2, 9, 12 and 14 would be ruled out since more QALYs can be achieved given the maximum willingness to pay. Similarly strategies 3 and 5 would be ruled out since their ICERs of £160,748 and £40,959 respectively, are far above the maximum threshold NICE recommends; the additional 0.1265 is judged to not be worth the extra £5,184, nor is the 0.1302 QALYs for the extra £5,804.

SENSITIVITY ANALYSIS

Five sources were thought to contribute most to the uncertainty surrounding the analysis; the utility values used in the analysis, the data used on the effectiveness of capecitabine monotherapy, the effectiveness of third-line therapy, possible price discounts and the calculation of overall survival. A number of scenarios were investigated and the results are outlined below:

o Utility values

An arbitrary 10% increase and decrease in all the utility values used in the model were tested and made no difference to the strategies that were dominated or to the ranking of the strategies in terms of cost-effectiveness. At a willingness to pay of £30,000 per QALY, strategy 15 (docetaxel, vinorelbine, capecitabine) was still the most cost-effective strategy, with the ICERs ranging from roughly £21,500 when all the utility values were increased (due to higher QALYs) to £26,250 when the utility values were decreased. At a willingness to pay of £20,000 strategy 14 remained most cost effective when utilities increased (with an ICER of £21,000) but when the utilities were reduced, strategy 9 (paclitaxel, capecitabine, no chemo) had the most favourable ICER at £17,923. When the utility ascribed to patients with toxicity was varied from the base-case value of 0.44 to 0.35 (to equal the utility associated with progressive disease with toxicity), this made little difference to the base-case results. Total QALYs (per patient) were slightly reduced with strategy 15 but it still had a favourable ICER of £23,687.

o Effectiveness of capecitabine monotherapy

The time spent without progressive disease having received capecitabine monotherapy was reduced by one third in the sensitivity analysis. This resulted in strategy 13 being included in the incremental analysis, when it had been dominated in the base case. Using a threshold value of £30,000 strategy 15 was still most cost-effective, maximising QALYs given the threshold and with an ICER of £25,359. Strategy 13 (docetaxel, capecitabine, vinorelbine) was associated with an ICER of £32,445. If a stricter threshold value was applied, say £20,000, strategy 2 (Docetaxel + capecitabine, then no chemo) was most cost-effective with an ICER of £8,325.

o Effectiveness of third-line treatment

Two 'effectiveness' parameters for third-line treatment were varied in the sensitivity analysis; the response and disease stabilisation, and the time spent free of progressive disease for responders, stable patients and non-responders. Both parameters were separately tested, reducing them by one third. When the response and stabilisation rates were reduced there was no change to the strategies that were dominated, or to the ranking of strategies. The conclusions from the base-case held, but the two most cost-effective strategies (when examining two different thresholds, £20,000 and £30,000 per QALY) were associated with slightly higher ICERs. The survival estimates proved to have more impact, since strategy 15 (docetaxel, vinorelbine, capecitabine) was dominated. Strategy 13 was associated with an ICER of £34,878 but the best strategy was strategy 14 (docetaxel, capecitabine, no chemo) with an ICER of slightly over £19,000 per QALY.

o Price discounts

A number of different price discounts for paclitaxel were investigated (50%, 60%, 70%, 80%, and 90%) and, as expected, changed the base-case results. Paclitaxel replaced docetaxel as the most cost-effective starting therapy, but after this the preferred sequences in terms of cost-effectiveness did not change from the base case. The ICERs associated with strategy 10 (paclitaxel, vinorelbine, capecitabine) ranged from £19,000 to just over £21,000. Paclitaxel followed by capecitabine then no chemotherapy yielded ICERs ranging from £16,300 to £14,250 and would be most cost-effective given a £20,000 per ICER threshold. A likely discount available on both paclitaxel (90%) and vinorelbine (45%) showed strategy 10 to have an even more favourable ICER (£18,666 per QALY), making it most cost-effective at a threshold of both £20,000 and £30,000 per QALY.

○ **Time from progression to death**

The time from progression to death (assumed to be 5 months in the base-case analysis) was varied from 4 – 6 months. This change, in either direction, had little effect on the base-case results serving to increase (6 months) or decrease (4 months) both the health benefits and the costs. Depending on the threshold value, either strategy 15 or strategy 14 would be considered most cost-effective.

Overall the sensitivity analyses showed that the results of the base case were reasonably robust to the parameters investigated. The main changes resulted from big potential price discounts, substituting docetaxel for paclitaxel as the preferred starting therapy. Other changes were noted when altering the effectiveness of third-line therapy and the 'progression-free' survival resulting from capecitabine, which was due to small differences in QALYs leading to different strategies being dominated and thus excluded from the incremental results.

DISCUSSION

The base-case results of this analysis provide a clear message for recommendations on this topic, in terms of cost-effectiveness. They show that docetaxel as a single agent therapy dominates the other taxane, paclitaxel, and any combination therapy involving gemcitabine, so all strategies but those starting with first-line docetaxel are ruled out in terms of cost-effectiveness. Using the threshold of £20,000, the most cost-effective strategy was docetaxel followed by capecitabine and then no further treatment (strategy 14). The GDG may consider there to be circumstances which justify the use of a higher threshold by which to judge cost-effectiveness and thereby accept strategy 15 which also starts with docetaxel but is followed first by vinorelbine and then capecitabine. This strategy is associated with higher quality-adjusted survival. Due to the multitude of strategies in the analysis, the results need careful interpretation. There is one strategy, strategy 13 (docetaxel followed by capecitabine then vinorelbine) that is narrowly excluded from the incremental analysis on the basis of extended dominance, but only by a tiny difference in total QALYs, 0.015. Given the uncertainty surrounding these point estimates, it is not clear which strategy is dominated and thus which should be excluded from the incremental analysis. If strategy 15 was dominated, leaving strategy 13 in the incremental analysis, strategy 13 would be associated with a favourable ICER of below £30,000 per QALY. On these grounds the analysis does not provide clear evidence on whether it is always preferable to give vinorelbine first followed by capecitabine.

Strategies 2, 9, 12 and 14 can be ruled out in terms of cost-effectiveness since more QALYs can be achieved given the maximum willingness to pay. Similarly strategies 3 and 5 would be ruled out since their ICERs of £160,748 and £40,959 respectively, are far above the maximum threshold NICE recommends; the additional 0.1265 is judged to not be worth the extra £5,184, nor is the 0.1302 QALYs for the extra £5,804.

The sensitivity analysis show there may however be circumstances in which the base-case results do not hold true. The presence of substantial discounts available nationally for paclitaxel show that if this discount is maintained and is available across England and Wales, the taxane of

choice would be paclitaxel rather than docetaxel, since these strategies yielded more favourable ratios of costs and health benefits. In response to doubts over the validity of the utility value for progressive disease, a 10% increase in this value was tested and it was found that the results were not sensitive to this increase.

There are a number of limitations to this analysis. No discounting was undertaken on either the costs or benefits attributed to each strategy. However this is unlikely to have a major bearing on the results since the patients live for a short time and treatment is the biggest contributor to costs which fall at the beginning rather than throughout the year. The sensitivity analyses conducted was rather limited and using an approach which does not fully capture the uncertainty surrounding the model. In addition some of the strong structural assumptions were not tested, and therefore their impact on the conclusions of the analysis is unknown. The interventions considered in the model were not exhaustive and whilst the most common sequences were included, there may be relevant comparators that have been excluded from the analysis.

Whilst a great deal of effort has been spent on obtaining consistent data on first-line treatment, by undertaking an indirect treatment comparison, many strong assumptions had to be made to combine evidence from different sources to inform the model on the relative effect of the full treatment sequences. Evidence on second-line treatment was poor, and even poorer for third-line treatment. The survival estimates from capecitabine monotherapy seem very high, higher even than first line treatment; although the results seem to be robust to a reduction in these by a third in the sensitivity analysis. No evidence existed for the 'No Chemotherapy' option, in particular this was not associated with any quality of life increase from the published utility values for progressive disease. Expert opinion from the guideline development group was used to fill in gaps in the data, but this has not been fully explored in the sensitivity analysis and some concerns remain as to the validity of the assumptions.

The costs used were often proxies for costs that were hard to capture and may not fully capture the differences between the different therapies, for instance the differences in i.v. times were not captured by costs (or utilities). It was also assumed that combination therapy was not associated with additional administration times, thus biasing the results in favour of the combination therapies. In addition it was no vial sharing was assumed, which may not reflect clinical practice.

Despite these acknowledged limitations, this analysis does provide some useful information for which the guideline development group can use in its deliberations over the recommendations to be made on this topic. Single agent taxane (either docetaxel or paclitaxel depending on the price discounts available) is the most cost-effective starting therapy. The combination therapies are much less cost-effective primarily due to the fact repetition of a chemotherapy agent later in the sequence was not allowed in this analytical model. Three lines of chemotherapy were shown to deliver more QALYs than one or two lines. The choice of which order to deliver capecitabine and vinorelbine is not as clear cut, and although the results show vinorelbine to be a more cost-effective second line treatment than capecitabine, the difference between the two strategies (13 and 15) is so small, the guideline development group should interpret this particular result with caution.

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4.7 The management of patients with metastatic HER2+ breast cancer that are having ongoing treatment with a biological response modifier.

Short summary

For patients undergoing therapy with a biological response modifier who experience disease progression there was only limited evidence on trastuzumab (TRZ) which comprised a RCT (von Minckwitz *et al.* 2008) a prospective post RCT study (Tripathy *et al.*, 2004) five retrospective case series (Fountzilas *et al.*, 2003, Gelmon *et al.*, 2004, Garcia-Saenz *et al.*, 2005, Montemurro *et al.*, 2006 and Stemmler *et al.*, 2005) and a phase II study (Bartsch *et al.*, 2006).

Limited data from a post-RCT analysis showed no significant improvements in safety or efficacy for women with disease progression who continued TRZ combined with different chemotherapies when compared with women in whom TRZ was given for the first time after their disease progressed on chemotherapy alone. Most case series also offered little evidence in support of continuing TRZ therapy beyond progression since, where relevant comparisons were made, no significant improvements were found for survival, efficacy or safety.

One retrospective case series demonstrated a significant survival advantage for women who had received both first and second line therapy with TRZ but, taken from a non-randomised study, the data was open to strong selection bias. Weak phase II evidence showed no significant difference in the length of time to progression between first, second or further lines of TRZ therapy which was interpreted as support for TRZ continuation.

A very recent, unpublished RCT showed that TRZ improved the efficacy of second line capecitabine in Her2 +ve patients with metastatic disease who had previously received TRZ in the adjuvant or first line setting. The response rate, clinical benefit rate, time to progression and overall survival were all statistically significantly superior for the combined therapy and with no additional significant toxicity. However, the data are as yet incomplete and insufficient to inform an economic analysis.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with metastatic HER2 +ve breast cancer who are having ongoing treatment with a biological response modifier and have disease progression	<ul style="list-style-type: none"> • Endocrine therapy without a biological response modifier • Chemotherapy treatment without a biological response modifier • Herceptin or lapatinib or bevacizumab alone • Herceptin and chemotherapy or endocrine 	Compare each intervention with each other	<ul style="list-style-type: none"> • Disease response • Progression free survival • Overall survival • QOL • Time to progression • Toxicity • Patient tolerability • Cost

POPULATION	INTERVENTION	COMPARISON	OUTCOME
	therapy <ul style="list-style-type: none"> • Herceptin and lapatinib • Herceptin and lapatinib and chemotherapy • Herceptin and bevacizumab • Herceptin and bevacizumab and chemotherapy • Lapatinib and chemotherapy or endocrine therapy • bevacizumab and chemotherapy 		effectiveness

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

The evidence comprises a prospective cohort study from the USA, four retrospective case series from Europe (n = 3) and Canada (n = 1) and a phase II study from Europe. Non-comparative studies and retrospective data analyses are, by design, only very weak evidence compared with, for example a RCT or other controlled study.

Overall survival

Montemurro *et al.* (2006) studied a group of MBC patients who had been previously treated with trastuzumab (T). Of the original 184 patients, 132 experienced disease progression and of these, 71 stopped TRZ treatment and were given either a variety of chemotherapies (n = 61) or endocrine therapy (n = 10). 40 patients remained on T-based therapy (5 had TRZ + endocrine therapy, 23 had TRZ + chemotherapy and 12 had TRZ monotherapy). The median overall survival (OS) for those patients continuing TRZ was 30.1 months (95%CI: 26.9-33.3) compared with 30.2 months (95%CI: 20.5-39.9) for patients who had stopped T. For 21 patients with rapid disease progression and who were unable to be treated except in the palliative setting, median OS was 7.4 months (95%CI: 4.6-10.3).

Fountzilias *et al.* (2003) performed a retrospective analysis of data from patients with progressive MBC who continued on T, either as a monotherapy or in combination with a variety of chemotherapeutic drugs. They reported median OS (from the time of the first TRZ therapy) as 22.2 months (95%CI: 16.3-28.2). Without a comparator, it would be difficult to assess the relative worth of TRZ continuation in this setting. Gelmon *et al.* (2004) also performed a retrospective analysis of data from patients progressing on TRZ who continued either TRZ as a monotherapy or in combination with various chemotherapeutic agents.

The median OS for all patients was reported as 29 months (95%CI: 22.7-56). The problem with all retrospective studies is that they are prone to selection bias. Data were only chosen from patients who were fit enough to continue treatment after progression or who had not been forced to stop TRZ therapy for reasons other than disease progression i.e. toxicity. For these patients,

TRZ continuation was presumably not an option and hence the introduction of bias – this should be considered if such studies are used to claim superior survival or tumour response after continuing TRZ therapy on disease progression.

Tumour progression

Montemurro *et al.* (2006) reported the median TTP for patients continuing TRZ therapy as 6.3 months (95%CI: 5-7.6) and for patients stopping TRZ therapy and continuing other treatment as 7.2 months (95%CI: 6.4-7.9).

Fountzilas *et al.* (2003) reports median TTP for each treatment group: TRZ monotherapy = 5.1 months (95%CI: 2.6-7.6), TRZ + PAC = 4.2 months (95%CI: 0-9.3), TRZ + VIN = 4.6 months (95%CI: 3.3-5.9), TRZ + GEM = 6.2 months (95%CI: 4.7-7.7 and TRZ + DOC = 4.1 months (95%CI: 0-11.6). The individual sub-group patient numbers are very low which does confound reliability.

Similarly, Gelmon *et al.* (2005) reported TTP by line and by sub-group: 1st line: TRZ monotherapy = 23 weeks (range: 3-73), TRZ + taxane = 24 weeks; 2nd line: monotherapy = 30.5 weeks (range: 18-68), TRZ + taxane = 24 weeks (range: 3-72) and TRZ + VIN = 26 weeks (range: 3-108). Evidence is also reported by Garcia-Saenz *et al.* (2005): 1st line: TRZ + chemotherapy = 6 months (range: 1->39 months), 2nd line: TRZ + chemotherapy = 3 months (range: 1->22) and 3rd line: TRZ + chemotherapy = 2 months (range: 1->12).

Bartsch *et al.* (2006) supplied data on TTP with confidence intervals and comparative statistics: 1st line = 6 months (95%CI: 5.4-6.6), 2nd line = 6 months (95%CI: 5.36-6.64) and beyond 2nd line = 6 months (95%CI: 5.32-6.68) (no significant difference). The authors claim that the maintenance of TTP supports a case for continued TRZ therapy on progression but the patient numbers were low and the lack of a control group weakens the strength of this evidence.

Tumour response

Tripathy *et al.* (2004) reported on H0649, an extension to the pivotal trial (H0648) which was the main study in the NICE technology appraisal 'Guidance on the use of trastuzumab for the treatment of advanced breast cancer'. H0648 patients were randomised to receive either TRZ with or without chemotherapy and, in this post-trial study, those patients experiencing disease progression either had their chemotherapy changed but remained on TRZ (group II, n = 93) or, if they had not previously received T, were offered TRZ usually with chemotherapy (group I, n = 154).

The overall response rate (ORR) was given as 14% (95%CI: 8.3-19.2) for group I compared with 11% (95%CI: 4.5-17) for group II. It's difficult to interpret this result since one cannot know whether patients who had not previously received TRZ had an accelerated tumour response or whether patients continuing with TRZ did not benefit as much as with their first TRZ regime such that the two groups 'caught up' with one another. Patients with minor responses or stable disease were 18% (group I) and 12% (group II).

Montemurro *et al.* (2006) only presented the tumour response results for the first TRZ regime but not for continuing patients.

Fountzilas *et al.* (2003) in the retrospective analysis, reports ORR for each line of treatment: 2nd line ORR = 24%, 3rd line ORR = 14%, 4th line ORR = 19% and 5th line ORR = 8%. Gelmon *et al.* (2004) also presented data in this way: 1st line ORR = 41%, 2nd line ORR = 36% (TRZ monotherapy) 1st line ORR = 38%, 2nd line ORR = 38% (TRZ + taxane) and ORR = 27% (TRZ + VIN) as did the authors of a third retrospective case series (Garcia-Saenz *et al.*, 2005): 1st line ORR = 39.7%, 2nd line ORR = 25.8%, 3rd line ORR = 12.5%, 4th line ORR = 0% (TRZ +

chemotherapy). Bartsch *et al.* (2006) reported tumour response for 2 lines and beyond: 1st line ORR = 42.6%, 2nd line ORR = 25.9%, beyond 2nd line ORR = 30%.

Adverse events

Only half the studies reported adverse events. Tripathy *et al.* (2004) observed 'severe' events in 5% of the total patient population, including asthenia (11%), back pain (6%), headache (9%), general pain (6%), leukopenia (8%) and dyspnoea (7%) in patients who had previously not been exposed to TRZ and asthenia (10%), back pain (6%), headache (6%), general pain (10%), leukopenia (11%) and dyspnoea (2%) in patients continuing on TRZ therapy (group I). There were no events reported for one group alone. Additionally, there was cardiac dysfunction in 9% of group I patients and 2% of group II patients.

Fountzilas *et al.* (2003) also reported 'severe' events in 5% or more of the total patient population, including neutropenia (25%), fatigue (12.5%), thrombocytopenia (1.5%), infection (10%), peripheral neuropathy (9%), myalgia & arthralgia (5%), nausea & vomiting (6%), stomatitis (6%), diarrhoea (6%), constipation (6%) and oedema (6%). In addition there were 8 cases of cardiotoxicity and 3 of LVEF reduction.

Gelmon *et al.* (2006) reported grade 3 adverse events: nausea & vomiting (1.9%), neutropenia (25.9%), thrombocytopenia (3.7%), anaemia (11.1%), stomatitis (3.7%) and hand-foot syndrome (5.6%) and one grade 4 event of neutropenia (9.3%). There was no cases of heart failure reported and only patient experienced a drop in LVEF which normalised after treatment.

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Montemurro F., Donadio M., Clavarezza M., Redana S., Jacomuzzi ME., Valabrega G., Danese S., Vietti-Ramus G., Durando A., Venturini M and Aglietta M (2006) Outcome of patients with HER2-positive advanced breast cancer progressing during trastuzumab-based therapy. *Oncologist* **11**: 318-324.

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Evidence tables

Question: Ongoing treatment with a BRM
Created by: Karen Francis on 25/10/2006 16:17:14

Tripathy <i>et al.</i> (2004)
Design: Prospective cohort study (prognosis), evidence level: 2 Country: United States
Inclusion criteria: Participation in H0648 Disease progression Her2 +ve MBC Normal (defined) haematological and non-haematological laboratory parameters Written informed consent.
Exclusion criteria: Pregnant or lactating
Population: Number of patients = 247
Interventions: Group I: TRZ at an initial dose of 4 mg per kg i.v. over 90 min on day 0 followed immediately by chemotherapy (if taken) then a weekly dose of TRZ at 2 mg per kg i.v. over 30 min directly before chemotherapy. Group II: TRZ at a continued dose of 2 mg per kg i.v. over 30 min on day 0 followed immediately by chemotherapy (if taken) then weekly at the same dose directly before chemotherapy. 71% patients overall received chemotherapy at the discretion of their treating physician: paclitaxel (30%), vinorelbine (23%), docetaxel (17%), fluorouracil (12%) and others, also hormonal therapy (14%) and radiation (35%) or a combination.
Outcomes: Primary: safety analysis. Secondary: efficacy (limited analyses)
Follow up: Tumour assessments were performed by the investigators, not independently and were timed according to their discretion. In some cases there was no such assessment and hence the efficacy analysis is incomplete, made from available data by the authors and not measured by formal criteria. All patients having received any amount of TRZ were included in the safety analysis. 52% patients in group I discontinued treatment because of disease progression compared with 41% in group II. 8% in group I withdrew due to adverse events, compared with 6% in group II. Two patients died from non-treatment related events, one in each group. One patient in group I experienced disease progression and did not receive T. By the end of study (October 1999) 69% of patients in group I and 65% in group II had died; all but two deaths were ascribed to MBC.
Results: Median treatment duration group I: 30 weeks (range: 0-185) Median treatment duration group II: 26 weeks (range: 0-184)

Number of patients on study treatment for > 24 months group I = 27%
Number of patients on study treatment for > 24 months group II = 18%

'Severe' (no grade given) adverse events in 5% or more of patients:

Group I: asthenia (11%), back pain (6%), headache (9%), pain (6%), leukopenia (8%) and dyspnoea (7%)

Group II: asthenia (10%), back pain (6%), headache (6%), pain (10%), leukopenia (11%) and dyspnoea (2%)

Cardiac safety:

9% of patients in group I experienced cardiac dysfunction (7 NYHA grade 1 or 2 and 7 NYHA grade 3 or 4) and of these, half (n = 7) had received prior anthracycline and half prior paclitaxel.

2% of patients in group II experienced cardiac dysfunction (1 NYHA grade 1 or 2 and 1 NYHA grade 3 or 4) and of these, all (n = 2) had received prior anthracycline with T.

The authors stated that there were no apparent trends of increased toxicity with continuation of TRZ and that no patients had developed antibodies against T. In addition, patients in group I that had experienced anthracycline related cardiac events during H0648 nevertheless had a good response rate and median survival rate in this post trial study and none had discontinued treatment for cardiac toxicity.

ORR group I: 14% (95%CI: 8.3-19.29: CR + 12 PR)

ORR group II: 11% (95%CI: 4.5-17.03: CR + 7 PR)

Minor response or stable disease group I: 18%

Minor response or stable disease group II: 12%

Median response duration group I: 7.4 months (95%CI: 5.1-12.5)

Median response duration group II: 6.7 months (95%CI: 4.1-10.2).

General comments:

This was an extension (H0649) to a phase III RCT (Slamon H0648) which was the pivotal study of the trastuzumab HTA. 469 women had been randomised to receive either chemotherapy alone or with trastuzumab (T). Following disease progression, all patients were offered TRZ and most also received chemotherapy.

154/234 patients in H0648 group I (chemotherapy only) now had TRZ with a new or additional chemotherapy and 93/235 patients in H0648 group II (chemotherapy plus TRZ) continued to receive TRZ and also had a new or additional chemotherapy. At the outset of this post-trial study patients were only given TRZ monotherapy but this practice was stopped quite quickly and chemotherapy was then started or resumed.

Group I patients in H0648 experienced a much lower median time to progression (30 months range: 1-106 months) than group II patients (45 months range: 7-134) and hence joined this post-study earlier.

Patients had Her2 over-expression: group I (22% 2+ and 78% 3+) and group 2 (23% 2+ and 77% 3+) by IHC and 75% FISH +ve in both groups.

The study design, purposely loose in structure to encourage enrolment, does not allow firm conclusions to be made about the efficacy of continuing TRZ beyond progression. It appears that the groups had similar outcomes in safety and efficacy (although no statistics were presented) which suggests that either the introduction of TRZ to group I may have improved their outcomes or that the continuation of TRZ in group II did not enhance their outcomes over and above what

had been already achieved. Without a theoretical third arm of patients who had TRZ withdrawn on disease progression, it is not possible to assess the contribution of TRZ alone.

Fountzilias *et al.* (2003)

Design: Retrospective case series (prognosis), evidence level: 3

Country: Greece

Inclusion criteria:

Previous therapy with trastuzumab (T) and chemotherapy with disease progression
Her2 over-expression of 2+ or 3+ (by IHC).

Exclusion criteria:

None stated

Population:

Number of patients = 80, age range 28 to 74 years, median age = 54 years

Interventions:

TRZ at an initial dose of 4 mg per kg i.v. over 90 min then weekly at 2 mg per kg i.v. over 30 min. In some patients this was modified to a three-weekly regime of TRZ at 6 mg per kg. TRZ was only withdrawn by patient request or at the discretion of the physician when toxicity was unacceptable.

Various chemotherapy drugs were also administered (no details of dosage): paclitaxel, vinorelbine, gemcitabine, docetaxel or triplet combinations with any of these. 28 patients were treated with TRZ monotherapy. Chemotherapy dosage was amended when indicated by haematological or other toxicity.

The most common 1st line combination was TRZ + paclitaxel (PAC) or docetaxel (DOC) (n = 60); the most common 2nd line was TRZ + vinorelbine (VIN) (n = 31) or TRZ + gemcitabine (GEM) (n = 21) and preferred 3rd line therapy was TRZ + gemcitabine (n = 13).

Outcomes:

Tumour response, time to progression (TTP), survival.

Adverse events.

Follow up:

Median follow-up time for surviving patients was 42.3 months.

Results:

Patients had Her2 over-expression 2+ (9%) and 3+ (91%)

2nd line: ORR = 24% (3 CR + 16 PR). SD = 28%. PD = 36% (n = 80)

3rd line: ORR = 14% (1 CR + 6 PR). SD 24%. PD = 43% (n = 49)

4th line: ORR = 19% (5 PR). SD = 31%. PD = 35% (n = 26)

5th line: ORR = 8% (1 PR). SD = 25%. PD = 33% (n = 12)

The remaining 3 patients had PD.

Median TTP for TRZ mono = 5.1 months (95% CI: 2.6 - 7.6)

Median TTP for TRZ + PAC = 4.2 months (95% CI: 0 - 9.3)

Median TTP for TRZ + VIN = 4.6 months (95% CI: 3.3 - 5.9)

Median TTP for TRZ + GEM = 6.2 months (95% CI: 4.7 - 7.7)

Median TTP for TRZ + DOC = 4.1 months (95% CI: 0 - 11.6)

Median OS from time of first TRZ therapy = 22.2 months (95% CI: 16.3 - 28.2).

Multivariate analysis of potential prognostic factors showed that the number of metastatic sites was significantly correlated with survival.

Adverse events

Severe toxicity seen in 5% or more of patients included neutropenia (25%), fatigue (12.5%), thrombocytopenia (1.5%), infection (10%), peripheral neuropathy (9%), myalgia & arthralgia (5%), nausea & vomiting (6%), stomatitis (6%), diarrhoea (6%), constipation (6%) and oedema (6%).

Cardiac events

There were 8 cases of cardiotoxicity: 3 of decreased LVEF, 2 of cardiac insufficiency, 2 of arrhythmia and 1 of pericarditis. All continued TRZ therapy without further event. Seven of these events occurred during first-line therapy and may have been related to anthracycline exposure.

General comments:

This retrospective analysis was performed on data from patients treated with trastuzumab and chemotherapy at 4 oncology centres in Greece between November 1998 and March 2002. Follow-up status was updated in September 2002 for all patients.

Her2 status was determined by IHC, not FISH. This determination was made by separate investigators, not centrally, and by using two different Her2 antibodies.

35% of patients had received adjuvant anthracycline therapy and 33% had received anthracyclines in the advanced disease setting.

This is a retrospective analysis of case file data with all the inherent weakness of this type of observational evidence.

Gelmon *et al.* (2004)

Design: Retrospective case series (prognosis), evidence level: 3

Country: Canada (federal state, Commonwealth Realm)

Inclusion criteria:

Women with MBC
Her2 overexpression
≥ 2 prior TRZ containing regimes

Exclusion criteria:

None stated

Population:

Number of patients = 105, age range 24 to 77 years, median age = 47 years

Interventions:

Trastuzumab monotherapy or with a taxane, vinorelbine or 'other' chemotherapy. No details of dosage, duration etc.

Outcomes:

Objective response rate (ORR), stable disease (SD), overall response rate (ORR + SD), time to progression (TTP), overall survival (OS).

Adverse events (cardiac and respiratory only).

Follow up:

Data were collected from case files: age, history, tumour characteristics, Her2 status, previous therapy, T-containing regimes date of last follow-up or death. Data were reviewed centrally.

Results:

Patients had Her2 overexpression 3+ (n = 75) and 2+ (n = 13) by IHC. Three patients were classed only as '-ve' and three as '+ve'. 21% of tumours had been tested using FISH and all were +ve.

Median OS for all patients = 29 months (95% CI: 22.7-56)

Efficacy 1st line (n = 77):

ORR for TRZ monotherapy (n = 27) = 41%

SD for TRZ monotherapy = 26%

Overall RR for TRZ monotherapy = 67%

Median TTP for TRZ monotherapy = 23 weeks (range: 3-73)

ORR for TRZ + taxane (n = 50) = 38%

SD for TRZ + taxane = 32%

Overall RR for TRZ + taxane = 70%

Median TTP for TRZ + taxane (n = 45) = 24 weeks (no range)

ORR for all first line = 39%

Efficacy 2nd line (n = 65):

ORR for TRZ monotherapy (n = 11) = 36%

SD for TRZ monotherapy = 27%

Overall RR for TRZ monotherapy = 63%

Median TTP for TRZ monotherapy (n = 10) = 30.5 weeks (range: 18-68)

ORR for TRZ + taxane 2nd line (n = 21) = 38%

SD for TRZ + taxane 2nd line = 29%

Overall RR for TRZ + taxane 2nd line = 67%

Median TTP for TRZ + taxane (n = 20) = 24 weeks (range: 3-72)

ORR for TRZ + vinorelbine (n = 33) = 27%

SD for TRZ + vinorelbine = 24%

Overall RR for TRZ + vinorelbine = 51%

Median TTP for TRZ + vinorelbine = 26 weeks (range: 3-108)

ORR for all second line = 32%.

10/30 patients who responded to the first regime also responded to the second and 9/21 patients who responded to the second regime had not responded to the first.

Adverse events:

22 patients had 24 cardiac events, non fatal. Two patients had lowered LVEF - one during the first and sixth TRZ based regimes and the other after 72 doses - treatment was stopped in both.

There was one case of pneumonia during which time a single TRZ dose was omitted.

General comments:

This paper describes a retrospective case review of women who, having had previous trastuzumab therapy had experienced disease progression. The patients had been treated at 13 centres in Canada, Europe and Australia.

The definition of stable disease was non-standard - i.e. if the notes 'suggested less than a PR and if treatment was continued for at least an additional 4 weeks'.

The evidence within this paper is very limited by design and no comparative statistics were presented. This is a retrospective review of data taken from a chosen selection of patients by the reviewers and which is therefore open to considerable bias. The lack of treatment detail and Her2

status determination is unhelpful.

Garcia-Saenz <i>et al.</i> (2005)

Design: Retrospective case series (prognosis), evidence level: 3- Country: Spain

Inclusion criteria: Histologically confirmed MBC Her2 overexpression of 3+ by IHC At least one previous trastuzumab-containing regime

Exclusion criteria: None stated

Population: Number of patients = 58, age range 26 to 76 years, mean age = 51 years, median age = 51years.

Interventions: Trastuzumab (T) was administered at 4 mg per kg i.v. over 90 min as a loading dose then weekly at 2 mg per kg i.v. over 30 min.
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Patients received chemotherapy at their treating physician's discretion. This was continued until progression at which time it was changed for another agent whilst TRZ was continued. Some patients also received hormonal therapy and/or RT.

Chemotherapeutic agents included: taxanes, vinorelbine, or 'other'. For the first regime, 6 patients received TRZ monotherapy.

Outcomes: Efficacy: objective response rate (ORR), time to progression (TTP), progression-free survival (PFS).
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Follow up: Data were collected from each patient file: age, menopausal status, hormonal status of tumour, previous therapy, number of metastatic sites, presence of visceral disease, previous chemotherapy number of chemotherapy lines, response rate, and progression-free survival.

ECG assessment of LVEF was performed at baseline. Subsequently, cardiac testing was done at the discretion of the physician.

No follow-up details.

Results: Efficacy 1st line (n = 58): ORR for TRZ + chemotherapy 1st line = 39.7% SD for TRZ + chemotherapy 1st line = 29.3% Median TTP for TRZ + chemotherapy 1st line = 6 months (range: 1 - >39 months).

Efficacy 2nd line (n = 31): ORR for TRZ + chemotherapy 2nd line = 25.8% SD for TRZ + chemotherapy 2nd line = 12.9% Median TTP for TRZ + chemotherapy 2nd line = 3 months (range: 1 - >22 months).
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Efficacy 3rd line (n = 8): ORR for TRZ + chemotherapy 3rd line = 12.5% SD for TRZ + chemotherapy 3rd line = 12.5%

Median TTP for TRZ + chemotherapy 3rd line = 2 months (range: 1 - >12 months).

Efficacy 4th line (n = 4):

ORR for TRZ + chemotherapy 4th line = 0%

SD for TRZ + chemotherapy 4th line = 25%

Median TTP for TRZ + chemotherapy 4th line = not stated.

General comments:

This retrospective study was made of data obtained from patients treated at a single centre in Spain between October 1999 and October 2003.

Definition of stable disease (no increase or decrease of disease of more than 12 weeks) is non-standard. There are no details of how tumours were assessed for disease or when or by whom.

Authors state that the ORR of 2nd line TRZ + chemotherapy was better for those patients who had already shown a response to the first regime (P = 0.03).

Authors included (in the analysis of first line therapy) 6 patients who had received TRZ monotherapy.

For first and second line therapies there are Kaplan Meier graphs which show (although this is not reported in the text) that PFS was approx. 7.7 months (1st) and 2.8 months (2nd).

This is very weak evidence with many factors expected of an observational study omitted. There are no details of follow-up, or drop-out rates and no adverse events reported.

Bartsch *et al.* (2006)

Design: Phase II study (prognosis), evidence level: 3

Country: Austria

Inclusion criteria:

Histologically confirmed MBC (89.8 DC and 10.2% LC)

Her2 over-expression 3+ (IHC) or FISH +ve

Disease progression following treatment with trastuzumab (T) based first line therapy.

Exclusion criteria:

None stated.

Population:

Number of patients = 54, age range 25 to 73 years, median age = 46 years

Interventions:

TRZ at an initial dose of 8 mg per kg on day 1 followed by three-weekly TRZ at 6 mg per kg.

Chemotherapy was given (no dosage details) commonly vinorelbine, docetaxel, capecitabine, gemcitabine, platinum derivatives or others.

Outcomes:

Complete response (CR), partial response (PR), stable disease (SD), time to progression (TTP) and disease progression (PD), overall survival (OS).

Adverse events.

Follow up:

Baseline CT-scan of chest and abdomen, mammography, ECG and gynaecological examinations were performed. Tumour assessments were made every three cycles and ECG on an irregular basis.

Study started in May 2002 and data were analysed in August 2005. Median length of follow-up of was 24 months (range: 7–51) overall (up to 7 lines of treatment).

2 patients were lost to follow-up and all were evaluated for efficacy and safety.

Results:

Tumour response:

1st line therapy: 7.4% CR + 35.2% PR + 42.6% SD. 14.8% PD (n = 54)

2nd line therapy: 3.7% CR + 22.2% PR + 42.6% SD. 31.5% PD (n = 54)

Beyond 2nd line: 1.7% CR + 28.3% PR + 28.3% SD. 41.4% PD (3rd line n = 33, 4th line n = 18, 5th line n = 6, 6th line n = 2 and 7th line n = 1)

Grade 3 adverse events: nausea & vomiting (1.9%), neutropenia (25.9%), thrombocytopenia (3.7%), anaemia (11.1%), stomatitis (3.7%) and hand-foot syndrome (5.6%)

Grade 4 adverse events: neutropenia (9.3%)

Median TTP 1st line: 6 months (95% CI: 5.4-6.6)

Median TTP 2nd line: 6 months (95% CI: 5.36-6.64)

Median TTP beyond 2nd line: 6 months (95% CI: 5.32-6.68)

Log rank analysis showed no significant difference between the groups. Data were not available for patients on 6th or 7th line therapies at the time of writing.

No symptomatic congestive heart failure was observed. One patient experienced a drop in LVEF to < 50% and had treatment withdrawn - the rate was normalised after treatment.

Median OS: not yet reached.

General comments:

This paper described a prospective phase II study. Patients who had experienced disease progression after first line T-based therapy continued with TRZ and alternative or additional chemotherapy.

Data have been presented by line of treatment and overall. The results suggest that although response rates fall off with each successive line this is no more than would be expected with any successive palliative treatment regime. The authors stated that the rate of modest decrease in clinical benefit, the lack of increase in TTP between treatment lines and the limited toxicity all offer evidence toward continuing TRZ therapy after disease progression. However, the patient numbers are low and there are no controls with which to compare these findings and so, however promising, these conclusions must be treated with extreme caution.

Montemurro *et al.* (2006)

Design: Retrospective case series (prognosis), evidence level: 3

Country: Italy

Inclusion criteria:

Women with Her2 +ve MBC

Previous TRZ therapy.

Exclusion criteria:

None given.

Population:

Number of patients = 184, age range 29 to 80 years, median age = 53 years

Interventions:

Initial therapy: details of dosage, other than that of trastuzumab (assumed therefore to be at standard dose) were given for all accompanying chemotherapies which included vinorelbine, docetaxel, paclitaxel, epirubicin, doxorubicin, 5-FU and combinations thereof.

Post-progression therapy: chemotherapy only group: vinorelbine, taxanes, CMF-like regimes, vinorelbine, anthracyclines, capecitabine, gemcitabine and combined therapies from above.

Outcomes:

Response rate (RR) to first post-progression treatment, overall survival (OS), time to (second) progression, post progression survival (PPS), disease-free interval (DFI).

Follow up:

Median follow-up for all patients was 17 months (range: 1-66).

Median duration of treatment was 7 weeks (range: 1-155).

132/184 patients progressed after initial TRZ based therapy, and 18 patients discontinued TRZ because of either unacceptable toxicity or at patient or physician request. 34 patients are unaccounted for in the analysis.

Results:

Patients had Her2 overexpression of 2+ (10%) and 3+ (80%) or not specified (10%). 70% of patients had prior exposure to anthracycline.

Of these 184 patients, 132 had progressive disease and 89 died of MBC. 21 of these patients progressed rapidly to the extent that they could receive only palliative care until death.

ORR of 1st TRZ based therapy = 55.4% (95% CI: 48.2-62.4)

ORR of 1st therapy if Her2 3+ = 57.4 (95% CI: 49.4-65.1)

ORR of 1st therapy if FISH +ve = 71% (95% CI: 59.4 - 80.4)

Median TTP from 1st therapy = 9 months (95% CI: 7.4-11.5)

Median DFI from 1st therapy = 21 months (range:0-752)

40 patients from the whole population continued with TRZ (12 with monotherapy, 23 with TRZ + chemotherapy and 5 with TRZ + endocrine therapy). 71 patients stopped TRZ and were treated with chemotherapy only (n = 61) or endocrine therapy (n = 10).

Survival analysis compared only the two chemotherapy groups (with or without T) and those patients who experienced rapid progression....

Rapid progression (n = 21):

Median OS = 7.4 months (95% CI: 4.6-10.3)

Median TTP = not evaluated

Median PPS = 2.4 months (95% CI: 1.9-2.9)

RR = not evaluated

Continuing TRZ (n = 40):

Median OS = 30.1 months (95% CI: 26.9-33.3)

Median TTP = 6.3 months (95% CI: 5.0-7.6)

Median PPS = 21.0 months (95% CI: 8.9-33.1)

RR = 17.9% (95% CI: 7.9 - 35.6%) (n = 28)

Stopping TRZ (n = 71):

Median OS = 30.2 months (95% CI: 20.5-39.9)

Median TTP = 7.2 months (95% CI: 6.4-7.9)

Median PPS = 18.7 months (95% CI: 12.3-25.0)
RR = 27.3% (95% CI: 18.0-39.0) (n = 66).

General comments:

This was a retrospective analysis of data collected from patients attending 7 clinics in Italy between September 1999 and September 2004. Patients included 60 on phase II clinical trials of TRZ + docetaxel, TRZ with docetaxel and epirubicin and with TRZ + docetaxel and liposomal doxorubicin as well as 124 patients receiving TRZ outside of clinical trials.

The authors, having separated those patients with very rapid progression from the other patient groups, have suggested that there is no obvious difference in survival outcomes between those receiving chemotherapy with or without T.

There are no statistical analyses presented.

Updated evidence (4.7)

Summary

Two papers were identified to update the evidence on continuing trastuzumab beyond disease progression: one retrospective study (Stemmler *et al.* 2005) and an unpublished non peer-reviewed abstract from the American Society of Oncology meeting in Chicago 2008 (Von Minckwitz *et al.* 2008).

The unpublished RCT (von Minckwitz *et al.* (2008) showed that TRZ improved the efficacy of second line capecitabine in Her2 +ve patients with metastatic disease who had previously received TRZ in the adjuvant or first line setting. The response rate, clinical benefit rate and time to progression were all statistically significantly superior for the combined therapy compared with capecitabine monotherapy and with no additional significant toxicity.

The case series demonstrated a significant survival advantage for women who had received both first and second line therapy with TRZ but, as a non-randomised retrospective study, the analysis was open to strong selection bias.

Reference

Von Minckwitz G., Zielinski C., Maartense E., du Bois A., Schmidt M., Eidtmann H., Cufer T., De Jongh FE., Andersson M., Stein R., Kaufman M., Nekljudovas V and Loibl S (2008). Capecitabine vs capecitabine + trastuzumab in patients with Her2 positive metastatic breast cancer progressing during trastuzumab treatment – the TBP phase III study (GBG26/BIG 3-05). Annual Meeting of the American Society of Oncology in Chicago, IL (USA) abstract 1025.

Stemmler HJ., Kahlert S., Siekiera W., Untch M., Heinrich B and Heinemann V (2006) Characteristics of patients with brain metastases receiving trastuzumab for HER2 overexpressing metastatic breast cancer. *Breast* **15**: 219-225

Evidence table

Question: Ongoing treatment with a BRM
Created by: Karen Francis on 22/07/2008

Stemmler *et al.* (2005)

Design: Retrospective case series (therapy). Evidence level: 3
Country: Germany

<p>Inclusion criteria: Women with Her2 +ve (3+ by IHC) metastatic breast cancer</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 136. Age range: 35 to 87 years. Median age = 58 years.</p>
<p>Interventions: Trastuzumab (TRZ) at a loading dose of 4 mg per kg followed by weekly doses of 2 mg per kg either as a single agent or combined with chemotherapy (at the discretion of the treating physician).</p>
<p>Outcomes: Tumour response (ORR = CR + PR) complete response (CR) partial response (PR) stable disease (SD) disease progression (PD) overall survival (OS)</p>
<p>Follow up: -</p>
<p>Results: First line MBC therapy (n=136): Endocrine therapy = 29 Chemotherapy = 107</p> <p>First line MBC TRZ-based therapy (n=66): TRZ monotherapy = 13 TRZ + taxanes = 25 TRZ + vinorelbine = 28</p> <p>Median duration of 1st line TRZ therapy = 29.5 weeks (range: 1-358) ORR = 37.9% (95%CI: 22.1-43.7)</p> <p>Second line MBC TRZ-based therapy (n=47): TRZ monotherapy = 3 TRZ + taxanes = 26 TRZ + vinorelbine = 15 TRZ + other agents = 3</p> <p>Median duration of 2nd line TRZ therapy = 25 weeks (range: 1-186) ORR = 35.7% (95%CI: 20.9-41.6)</p> <p>23 of these women had TRZ after disease progression with a TRZ-based first line therapy. All had received TRZ + vinorelbine or taxanes (first or second line), TRZ combined with gemcitabine, cisplatin or with capecitabine.</p> <p>Median duration of TRZ based treatment beyond progression = 55 weeks (range: 5-156) ORR of first TRZ based regimen in these women = 56.6% (95%CI: 30.1-74.2) ORR of second TRZ based regimen in these women = 39.1% (95%CI: 17.6-60.7)</p> <p>Median OS for whole population = 42.7 months (range: 1-112). There was no significant difference in response rates or median survival for those patients who had received first line TRZ compared with those who had not and the choice of drug combined with TRZ was also not significant.</p> <p>Women who received TRZ beyond disease progression, having received TRZ at first line as well, experienced a significant advantage in terms of survival compared with those patients who had</p>

only received one TRZ regime (38.5 vs 62.4 months P = 0.01).

General comments:

This paper describes a retrospective analysis of case files of women with Her2 +ve metastatic breast cancer treated in three wards of a single hospital between March 2000 and May 2004. 41% of women had received prior adjuvant anthracyclines, 19.9% taxanes and 9.6% both. The majority of women had visceral metastases.

Women who had received both first and second line TRZ based therapies had a significant survival advantage compared with women who had received only one line of TRZ, either at first or second line. This finding was interpreted as support for continuing TRZ beyond disease progression. However, the number of women who received two lines of TRZ was only 23, much lower than the number of women who had not (n=113). In addition, no patient demographics were presented and it is therefore not possible to say that these arms were balanced – the two groups were not initially randomised and may have had completely different survival prognoses. Hence although statistically proven the findings may not translate to clinical benefit.

Von Minckwitz *et al.* (2008)

Design: Randomised controlled trial (therapy). Evidence level: 4 (ASCO abstract)

Country: United States of America

Inclusion criteria:

Women with Her2 +ve locally advanced or metastatic breast cancer
Disease progression during treatment with trastuzumab (TRZ) with or without adjuvant and/or 1st line chemotherapy for advanced disease
LVEF ≥ 50%

Exclusion criteria:

None stated

Population:

Number of patients = 156. Age range: 30 to 82 years. Median ages = 52.5 (CAP + TRZ) or 59(CAP)

Interventions:

[1] Capecitabine (CAP) at 2,500 mg per m² in two equal doses per day on days 1-14 every 22-day cycle

[2] CAP as above + trastuzumab (TRZ) at 6mg per kg every 22 days.

Outcomes:

Time to progression (TTP) overall survival (OS) objective response (complete response + partial response) clinical benefit (objective response rate + stable disease > 24 weeks) and safety.

Follow up:

Median follow-up = 15.6 months

Results:

Median TTP for CAP after 65 events = 5.6 months (95%CI: 4.2-6.3)
Median TTP for CAP + TRZ after 62 events = 8.2 months (95%CI: 7.3-11.2)
HR = 0.69 (95%CI: 0.48- 0.97) P = 0.0338

Brain metastases were observed in 5 patients in the CAP arm and 8 patients in the CAP + TRZ arm.

Median OS for CAP after 38 events = 20.4 months (95%CI: 17.8-24.7)
Median OS for CAP + TRZ after 33 events = 25.5 months (95%CI: 19.0-30.7)

HR = 0.76 P=0.26 (NSD)

Overall response rate for CAP = 27% (95%CI: 17.3-38.6)

Overall response rate for CAP + TRZ = 48% (95%CI: 36.5-59.7) P = 0.011

Clinical benefit ratio for CAP = 54% (95%CI: 42.1-65.7)

Clinical benefit for CAP + TRZ = 75.3 (95%: 64.2-84.4) P = 0.0068

Primary disease progression was seen in 23% of CAP patients and 15.6% of CAP + TRZ patients.

Grade 3/4 adverse events CAP% vs CAP+TRZ%:

Neutropenia = 4.4 vs 5.3

Febrile neutropenia = 0 vs 2.6

Vomiting = 4.1 vs 1.3

Diarrhoea = 1.8 vs 15.6

Mucositis = 2.7 vs 1.3

Hand-foot syndrome = 24.3 vs 32.5

Nail changes = 0 vs 4.9

Sensory neuropathy = 5.4 vs 2.6

Fatigue = 5.4 vs 3.9

Cardiac = 2.7 vs 5.2

There were no treatment related deaths. One CAP + TRZ patient had a LVEF < 40.

General comments:

Women were enrolled between January 2004 and May 2007 but the enrolment was terminated prematurely when lapatanib was registered. This study was therefore underpowered since it was intended to enrol 482 patients in order to identify a significant difference between study arms. Patients were randomised into the two treatment arms stratified on adjuvant and prior first line therapy for advanced disease.

11/156 women had received first line TRZ with a taxane, 42 had received first line TRZ monotherapy or in combination with chemotherapy and 3 patients had received TRZ and a taxane as adjuvant therapy.

The preliminary details of this trial were presented at a scientific meeting in 2008 and the data are not yet published in a peer reviewed journal. The authors concluded that TRZ improved the efficacy of 2nd line CAP in Her2 +ve patients with MBC. The response rate, clinical benefit rate and TTP were all statistically significantly superior with the combined therapy compared to CAP alone and with no additional significant toxicity. However, the data are as yet incomplete and insufficient to inform an economic analysis.

Chapter 5 – Community-based Treatment and Supportive Care

5.1 The ongoing management of advanced breast cancer patients in the community setting

Short summary

One moderate quality but dated RCT (Mor *et al.*, 1988), three small RCTs (Hall and Lloyd, 2008, Smith *et al.*, 1994 and Majid *et al.*, 1989) and one high quality Canadian systematic review (Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante, 2004) looked at several forms of home therapy vs in-patient treatment for patients with cancer. Only one paper specifically looked at breast cancer patients (Hall and Lloyd, 2008).

None of the studies identified a significant clinical advantage with regard to treatment in the community compared with the hospital nor was there a difference in patient quality of life, as measured by standard scales. However, there was broad agreement across studies that patient satisfaction was considerably higher with treatment in the home or community compared with the hospital in-patient experience.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with advanced cancer	<ul style="list-style-type: none"> Any therapy given intravenously, including by Port-a-Cath or central access, administered to a patient at... The patient's home or At a community facility (GP practice, community hospital) or At an oncology centre (cancer units) 	Intravenous therapies administered to a hospital in-patient	<ul style="list-style-type: none"> Safety / complication rate (including infection e.g. MRSA) Success / failure rates leading to transfer to centre Patient satisfaction (incl. treatment in preferred place of care, choice of treatment, confidence in communication) QOL No of cycles of treatment delivered Reduced no. of visits/waiting time for hospital tests & treatment

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

The evidence base for this topic is poor. No papers specifically addressed the needs of breast cancer patients in respect of home intravenous therapy. Although the four included papers are different in content, they are consistent in their findings. None of the studies identified a significant clinical advantage with regard to treatment in the community compared with the hospital nor was there a difference in patient quality of life, as measured by standard scales. However, there was broad agreement that patient satisfaction was significantly higher with treatment in the community environment as opposed to the experience as a hospital in-patient. Evidence about costs was contradictory and probably of little evidential value since none of the studies originated in the UK and in some cases the figures and study regimes are quite outdated.

One moderate quality RCT (Mor *et al.*, 1988) randomised 442 cancer (mixed type) patients to either treatment as a hospital in-patient or as a visitor to a purpose built facility within the hospital, the Adult Day Hospital. This facility included nursing access, pharmacy, lounge and education centre where patients received treatment from their own physician and were then obliged to return home or, if this was indicated, be admitted to the main hospital. 9, 16 and 22 days after randomisation, patients and their families completed many questionnaires which covered issues including quality of life, satisfaction and understanding of treatment. Medical staff also furnished details about clinical outcomes and the data were compared with those from patients being treated in the main hospital.

This study found that there were no statistically significant differences between: psychosocial status of patients and family, the number of family-provided direct hours of care, subjectively assessed family disruption, reported time lost from work, overall survival, response to treatment rate (in those patients with measurable or evaluable disease), laboratory parameters or symptoms experienced. Those parameters which scored significantly higher in favour of the ADH regime were: patient assessment of facilities, nurse's self-care instructions, helpfulness of staff, access to follow-up care and attractiveness of the environment. It was also found that ADH medical costs were approximately one third lower than those of a hospital in-patient. This study dates to 1988 and therefore the statistics and conclusions may not be relevant to the current treatment settings.

A second smaller RCT (Smith *et al.*, 2004) randomised 37 patients with multiple myeloma to receive three months of intravenous pamidronate (a bisphosphonate) in either the home or hospital setting. These patients then crossed over to the other arm and repeated the treatment for a further three months. Patient preference (visual analogue scale of 1-100) and quality of life (EORTC QLQ-C30) were assessed at baseline and after 3 and 6 months.

Patient preference was statistically significant higher for home treated patients: 91.8/100 vs 69.7/100 ($P < 0.05$). The EORTC questionnaire results showed no significant differences between home and hospital patients scores for functional domains (physical, role, emotional, cognitive, social), symptoms domain (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) or global health status, however, 81% of patients stated a preference for treatment in the home setting. Although no data are presented the nurse survey suggests that home treatment took a considerable amount more of their time, which might have a negative cost implication for this regime.

A large and thorough systematic review, performed by the Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) in Quebec (2004), examined cancer patients who were in receipt of any form of home treatment whether intravenous, oral, subcutaneous etc. compared with in-patient treatment. The review excluded studies whose participants with advanced, terminal disease being treated with chemotherapy and in addition, although of good quality, only a small part of this review may be relevant for this question as many of the issues examined were of national interest only.

The authors found no clinical benefit to home treatment compared with hospital therapy but also pointed out that this was possibly due to the lack of good papers reporting this outcome. It was also apparent that safety was not a significant problem with home treatment but added that uncommon adverse reactions may not have been observed given the limited patient number in the included studies.

The authors concluded that home chemotherapy had a cost shifting effect, from in-patient to out-patient facilities or from out-patient facilities to home care agencies and visiting nurse organisations. The evidence for the financial effect on patients was lacking. They could demonstrate no consensus on whether either regime was more cost effective than another since their included studies differed in the findings for this outcome.

A small RCT (Majid *et al.*, 1989) examined intravenous 5'-fluorouracil given as part of an induction chemotherapy regime to twenty-two men and women with advanced head and neck cancer. Study participants were randomised to receive their therapy either in their own home or as a hospital in-patient. The design of the study was such that after the first cycle of therapy patients were to cross to the other arm to receive the next cycle. However, 42% of patients initially randomised to receive their first cycle in hospital refused to accept home therapy thereafter ('non-acceptors'). No statistical data were presented but patient scores for psychological distress according to the Profile of Mood State questionnaire, which was completed at baseline and after each chemotherapy cycle, were tabulated.

The major concerns of the 'non-acceptor' in-patient group, when asked why they had refused home treatment were: fear of pump malfunction, managing problems (not specified), inability to participate in activities at home, physical adjustment to wearing the apparatus and returning to hospital (for checking the apparatus) and not having access to medical staff. Having round-the-clock medical care and prepared meals were seen as the main advantages of in-patient treatment.

The out-patient 'acceptors' reported little adjustment needed to wearing their apparatus and one patient was even able to return to work in this way. 78% patients reported being able to do light housework and entertain their friends whilst wearing the apparatus and 66% participated in hobbies, drive or use public transport to the same level as they experienced prior to their illness and 50% of patients reported being able to visit friends and do their own shopping. The group reported the main advantages of out-patient treatment as being able to continue with their work, feeling mentally better at not being in hospital and operating on their own schedule.

The different attitudes and concerns of the 'non-acceptor' group may have been due to the different (but not statistically tested) patient characteristics with regard to marriage status, education and general performance status (i.e. lack of normal diet and/or work activity) prior to the study.

References

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Evidence tables

Question: Intravenous therapies in the community or as an in-patient?
Created by: Karen Francis on 13/08/2007

Mor <i>et al.</i> (1988)
Design: Randomized controlled trial (other), evidence level: 1- Country: United States
Inclusion criteria: Patients must have had 4-8 hour treatment plan including chemotherapy or other long-term i.v. treatment A family member or other individual helping with home care Transportation available to and from the ADH Stable cardiovascular and respiratory status Mental competence No requirement for skilled overnight nursing Where ADH was the only alternative to admission as an in-patient Isolation care was not required
Exclusion criteria: Patients for whom standard out-patient care was possible.
Population: Number of patients = 442
Interventions: Adult Day Hospital (ADH) (n = 229) In-patient (n = 213) Adult Day Hospital: a 12-bed pilot unit was constructed within the hospital. The facilities included nursing core, treatment room, two follow-up rooms, education centre, satellite pharmacy, waiting lounge and administrative offices. The ADH was designed to create a relaxing and comfortable environment facilitating communication among patients, families and staff. A physician director was responsible for clinical management of the unit but patients were dealt with by their own physician. No house staff were assigned to the unit. There was telephone access to a nurse 24hrs a day, 7 days a week. There was no overnight accommodation so that patients unable to return home for medical reasons had to be admitted to the main hospital. In-patient care: standard care - no details given. Treatment strata: Cisplatin > 100 mg per m ² (n = 40) Low dose cisplatin (n = 73) Methotrexate-vinblastine-Adriamycin-cisplatin (n = 69) Other chemotherapy (n = 140) Other treatment (n = 92)
Outcomes: To compare ADH care with usual in-patient care for cancer patients. The clinical, psychosocial

(and cost) outcomes were evaluated over a 60 day period.

At ~9 days post-randomisation, patients were contacted for the collection of demographic data. At ~22 days post randomisation, patients were interviewed by telephone and asked to give details of perceived satisfaction, anxiety level, symptoms, compliance with symptom relief instructions and quality of life. At ~67 days post-randomisation, patients and their helpers answered additional questions testing their knowledge of the disease and its treatment together with data relevant to economic analysis. Medical data were obtained from patient charts. The following parameters were measured: therapeutic response (physician ratings), toxicity (WHO ratings), symptom experience (McGill/Melzack pain scale), KPS, quality of life (Spitzer QLI), mood states (Profile of Mood States), patient satisfaction with care (modified Rand Satisfaction with Medical Care Scale), family involvement (mean no of hours per day provided to patient), family disruption (factor-based scales), patient and helper chemotherapy knowledge, patient compliance and patient assessment of facilities (modified Likert Scale from 1 (worst) to 7 (best)).

Follow up:

During the 60 day study period 13 ADH (5.7%) and 15 (7%) in-patients died.

191/229 ADH patients and 180/213 in-patients completed the 20-day questionnaire. Attrition rates between arms appeared to be similar and were due to death, treatment cancellation, removal from study, refusal to continue (patient or family), language barrier, failure to receive treatment within 20 days and living too far away from the hospital.

Results:

No statistically significant differences were found between:

- 1) Psychosocial status of patients and family (ADH 198/229 (87%) vs inpatient 188/213 (88%).
- 2) The number of family-provided direct hours of care, subjectively assessed family disruption, or reported time lost from work.
- 3) The time lost from work between employed patients in ADH and inpatient groups.
- 4) Overall survival
- 5) Response to treatment rate (in those patients with measurable or evaluable disease)
- 6) Laboratory parameters
- 7) Symptoms experienced

Patient assessment of facilities (ADH vs in-patient care):

Nurses self-care instruction: 5.9 vs 4.5 (P < 0.001)

Helpfulness of staff: 6.6 vs 5.3 (P < 0.001)

Access to follow-up care: 6.1 vs 5.5 (P = 0.03)

Attractiveness of the environment: 6.7 vs 6.1 (P = 0.001)

The major difference between ADH and in-patient treatment was in medical cost which was approximately one-third lower for ADH patients (P< 0.001) than for the in-patient group.

General comments:

This paper presented a 2 year single centre study which started in 1984. Approximately 70% of the patients were men and there may have been no women with breast cancer included in this study.

The study design was a stratified random assignment trial using a sealed envelope randomisation method, undertaken by the ADH administrator.

ADH patients received chemotherapy, immunotherapy or other intravenous treatments extending over periods of at least 4 hours but rarely more than 8 hours. Treatment was prescribed and supervised by the patients' physicians. Hospital in-patient treatment was not detailed but is assumed to be the same.

Outcome measurements were made over a 60 day period. Analysis was stratified by treatment

regime because one of the primary outcomes of this study was the practical and economic feasibility for each regime.

Although there were initial concerns among physicians about having to treat their patients in the ADH setting, by the end of the two year study period, 76% of active medical oncologists in the hospital had their patients admitted to the facility.

The authors concluded that the study demonstrated that day hospital care of medical oncology patients was clinically equivalent to in-patient care, caused no negative psychosocial effects and cost less than in-patient care. They felt that the findings showed a trend toward de-hospitalisation of medical treatment.

Analyses of cost, clinical and psychosocial outcomes were performed on different sub samples of patients. Cost analyses included patients who died or were removed from study. Other analyses seemed to 'lose' patients or not include all data.

Since this study was conducted some time ago (before 1988), the results may not apply to treatment protocols used today.

Smith *et al.* (2004)

Design: Randomised crossover trial evidence level: 1

Country: UK

Inclusion criteria:

Age < 80 years

Life expectancy > 6 months

Symptomatic stage II or III multiple myeloma either at plateau phase or receiving active treatment

Settled home environment

Written informed consent

Exclusion criteria:

Concomitant use of other trial drugs or bisphosphonates

Population:

Number of patients = 37, age range 36 to 80 years, mean age = 65 years

Interventions:

Six 4-weekly cycles of pamidronate at 90 mg infused i.v. over 90 min, given for the management and prophylaxis of multiple myeloma. Treatment was given either in the home or at hospital.

Patients were randomised to receive iv treatment for 3 months in one setting before crossing over to the other arm for a similar 3 months of treatment.

Outcomes:

Patient/carer preference for treatment (assessed on a visual analogue scale from 0 (not acceptable) to 100 (extremely acceptable)) quality of life (QOL - assessed by the EORTC QLQ-C30 tool).

EORTC QLQ-C30 measures functional scales, global health status and quality of life (where high scores are optimal) and symptoms scales (where low scores are optimal). In all cases the range of scores is 0-100 and numerical differences between arms can be analysed for statistical significance.

Follow up:

The EORTC-QLQ-C30 questionnaire was completed at baseline and at the end of each 3-month treatment period.

34/37 patients completed the hospital phase and 33/37 completed the home treatment phase.

Of the 18 patients randomised to the hospital arm, 2 patients died of progressive disease and 1 patient withdrew consent having experienced adverse events. Of the 19 patients randomised to the home treatment arm, 2 patients withdrew because of co-existing morbidity (one subsequently died of disease progression).

Results:

Patient/carer preference for treatment (scale of 0-100):

Home care treatment = 91.8

Hospital treatment = 69.7

mean difference (home care – hospital care) = 22.2 (95%CI: 11.1-33.3) (P < 0.05)

At the close of the study, when patients were asked to state a preference for treatment location 81% of patients stated that they preferred the home setting (P < 0.001)

EORTC QLQ-C30:

Functional (physical, role, emotional, cognitive, social) = nsd between home and hospital treatment

Symptoms (fatigue, nausea & vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) = nsd between home and hospital treatment

Global health status/QOL = nsd between home and hospital treatment

The low patient number, even for a crossover trial, may have contributed to the lack of significance.

There were no reports of adverse events which could be considered to be due to the location of treatment administration.

General comments:

This paper presents results from the Pilot Aredia Treatment at Home (PATH) study which was a prospective, open label, randomised, crossover multicentre (n = 4) trial of treatment with intravenous pamidronate in the home or hospital setting.

Home treatment was given by an appropriately trained nurse, usually the hospital clinic nurse. In one centre the infusions were given by an outside agency but in the presence of the clinic nurse. Hospital treatments were according to standard practice, integrated into a regular day ward or clinic setting according to the individual centre.

According to the authors, there were some differences between centres in the proportions of patients with stable or progressive disease – further details were not given. Such bias may have affected the quality of life outcomes.

This is a small study which suggests, at least for this group of participants, that home treatment is the preferred option for patient satisfaction although this is not supported by the structured evaluation tool. The majority of clinical nurses, when asked, said that the home treatment had taken more time than the hospital treatment. The approximate measure of how much more time ranged between < 25 and up to 100%, a factor that could affect cost-benefit ratios.

Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) (2004)

Design: Systematic review evidence level: 2++

Country: Canada

Inclusion criteria:

None stated

<p>Exclusion criteria: Excluded studies: Studies focused on terminally ill patients receiving chemotherapy as palliative care Studies of home-based, high dose chemotherapy and stem cell rescue for MBC and other cancers</p>
<p>Population: Number of patients = N/K</p>
<p>Interventions: Home chemotherapy, including any type of administration of chemotherapeutic agents (intravenous, subcutaneous, oral etc) at home with or without the supervision of a nurse.</p>
<p>Outcomes: Outcomes that might be relevant: clinical benefit, cost reduction, safety and patient quality of life.</p> <p>Outcomes that are probably not relevant and are not included here: organisational implications for the healthcare system (of Canada), ethical, legal and social implications (for Canada), and influence of patient and regional characteristics on viability as a service.</p>
<p>Follow up: N/A</p>
<p>Results: Clinical benefit: The authors found a lack of evidence for the effect of home chemotherapy on clinical outcomes since most of the eight identified studies related to specific protocols rather than to the treatment settings e.g. oral (in the home) vs intravenous (in a hospital) chemotherapy as opposed to the same therapy administered at hospital or in the home.</p> <p>Cost reduction: The authors found only one study that provided convincing evidence in support of cost savings for home chemotherapy compared with in-patient therapy. However, this study was a US paediatric crossover trial with just 14 participants. Two studies found home chemotherapy to be more expensive than in-patient treatment. The additional cost was attributed mainly to nursing labour (care and co-ordination), travel time, transportation and special equipment. Because of these variable results the authors concluded that home chemotherapy has a cost shifting effect, from in-patient to out-patient facilities or from there to home care agencies and visiting nurse organisations. The evidence for the financial effect on patients was lacking.</p> <p>Safety: The authors summarised the results from seventeen papers in a table, a modified version of which (excluding paediatric studies or studies not involving iv therapy), is shown below. The conclusion was that, notwithstanding the generally small sample size of most included studies, home chemotherapy can be provided safely. However, they add that the strict selection criteria used to determine patient eligibility might make this conclusion unsurprising and also that rare adverse reactions might not be observed in small patient number studies.</p> <p>The authors point out that for half of the studies involving intravenous chemotherapy a nurse either administered the treatment or daily visits by a nurse were provided, which presumably would have reduced the risk to the patient.</p> <p>Quality of life: The authors concluded that the evidence for this issue was limited by the small number of controlled studies and participants. The evidence that was identified in controlled studies did not demonstrate an improved quality of life in favour of home treatment, except for paediatric patients and their parents. Uncontrolled studies had generally positive findings in favour of home treatment</p>

Patient preference:

The authors presented results from studies reporting on patient preference with home care, satisfaction and other psychosocial issues such as independence, concerns, needs and levels of stress. Nine out of eleven studies reporting on patient preference and choice presented strong evidence in favour of home treatment. Seven out of the nine studies which reported patient satisfaction presented results which favoured home therapy or some part of thereof.

General comments:

This is a thorough systematic review which is only partly relevant to the topic question e.g. studies recruiting patients with metastatic disease were excluded but all studies of all types of chemotherapy (e.g. subcutaneous, oral administration etc) are included. Some of the outcomes are specific to Canada and were the results of semi-structured qualitative interviews with service providers or administrators from the Canadian health system. However, some outcomes of this review are relevant and have been included in this evidence base. The review was presented in narrative form and there were no data analyses.

The overall conclusions were that there was insufficient evidence on the clinical benefit or cost effectiveness of home chemotherapy compared to non-home settings but more evidence to show that home treatment could be delivered safely with few serious complications or accidents, providing patients were carefully selected and trained. Evidence in favour of improved quality of life is anecdotal but preference for, and satisfaction with, home chemotherapy is strongly supported with the proviso that study participants may have been required to be accepting of the methodology in order to be recruited thus introducing an element of selection bias.

Magid *et al.* (1989)

Design: Randomized controlled trial (other), evidence level: 1-

Country: United States

Inclusion criteria:

Patients with locally advanced head and neck cancer (stage III or IV) with no distant metastases
 No prior therapy
 Performance status ≥ 2

Exclusion criteria:

None stated

Population:

Number of patients = 22, median age = 56 years

Interventions:

3 or 4 cycles of induction chemotherapy given in the home or as a hospital in-patient:

The initial treatment was methotrexate at 120 mg per m² on day 1 followed by leucovorin rescue and cisplatin at 100 mg per m² on day 2 (all patients in the study received this regime in the hospital) followed by a 5-day continuous infusion of 5'-FU at 1000 mg per m² per day.

For all patients, 5'-FU infusion was given via an implantable permanent venous access device (Port-a-Cath). For home patients, the drug was delivered by an Infusor, a portable and disposable drug delivery system changed daily by the patient and for hospital in-patients, by the Flo-Gard volumetric infusion pump.

Patients were randomised after receipt of the initial chemotherapy to receive their first cycle of 5'-FU in the home or as an in-patient. The patients were then to cross over to the other arm for the second cycle of chemotherapy. Some patients refused the option of home therapy for all of the 3 cycles of 5'-FU and were labelled as 'non-acceptors' but any patients receiving any cycle in the

home were labelled as 'acceptors'.

Outcomes:

Psychological distress (Profile of Mood State, POMS).

Follow up:

Baseline data were collected after randomisation: sociodemographics, availability of social support, functional status and daily functioning. Patients also related their concerns regarding their cancer and treatment and completed a standardised measure of psychological distress (POMS).

Follow-up interviews were conducted 24 hours after the 3rd therapy cycle. This included patient evaluation of home and in-patient treatment, rating the advantages, disadvantages and problems of either treatment regime together with overall satisfaction, adjustment and activity level during treatment. The POMS questionnaire was repeated. Patients who consistently refused home therapy were asked to state their reasons for refusal.

3/22 discontinued therapy during the first treatment cycle due to either medical complications or progressive disease.

Results:

8/19 evaluable patients declined to receive any treatment in the home ('non-acceptors') and therefore there were 11/19 'acceptors'. Of these, 2/11 were not evaluated after their third treatment cycle - one patient died and the other refused to be interviewed.

Patients experienced mild/moderate myelosuppression and mucositis with both delivery mechanisms with no significant differences in frequency or severity of side effects between the two methods.

There were no significant differences in the toxicities experienced with chemotherapy between treatments at home 'acceptors' and 'non-acceptors'.

Comparison of Mood States (baseline vs cycle 2):

Non-acceptors:

Tension: 9.43 (n =7) vs 11.88 (n = 8)
Depression: 6.17 (n = 6) vs 8.75 (n = 8)
Anger: 7.29 (n = 7) vs 5.38 (n = 8)
Fatigue: 4.0 (n = 7) vs 8.0 (n = 8)
Confusion: 5.57 (n = 7) vs 6.0 (n = 8)

Acceptors:

Tension: 9.2 (n = 10) vs 9.75 (n = 8)
Depression: 5.9 (n = 10) vs 8.0 (n = 8)
Anger: 2.6 (n = 10) vs 5.5 (n = 8)
Fatigue: 5.5 (n = 10) vs 9.5 (n = 8)
Confusion: 5.4 (n = 10) vs 7.5 (n = 8)

Baseline levels of tension, depression, anger and confusion were not stated to be statistically significantly different between groups at any point. Group scores suggested that scores for all parameters were lower in the out-patient group than for third cycle in-patients but, again, no statistics were offered in support of significance or otherwise.

The major concerns of the 'non-acceptors' in-patient group when asked why they had refused home treatment were: fear of pump malfunction, managing problems (not specified), inability to participate in activities at home, physical adjustment to wearing the apparatus and returning to hospital (for checking the apparatus) and not having access to medical staff. Having round-the-clock medical care and prepared meals were seen as the main advantages of in-patient

treatment.

The out-patient group 'acceptors' reported little adjustment needed to wearing their apparatus and one patient was even able to return to work in this way. 78% patients reported being able to do light housework and entertain their friends whilst wearing the apparatus and 66% participated in hobbies, drive or use public transport to the same level as they experienced prior to their illness. 50% of patients reported being able to visit friends and do their own shopping. The group reported the main advantages of out-patient treatment as being able to continue with their work, feeling mentally better at not being in hospital and operating on their own schedule.

General comments:

This paper reports a small (n = 22) RCT undertaken between September 1985 and April 1987. Patients were initially randomised (methods unknown) to receive intravenous chemotherapy in the home or as a hospital in-patient. The study was designed such that patients then crossed over to the arm but this did not happen in practice since 42% of patients refused to accept any home treatment.

There were very obvious differences (but not necessarily of statistical significance) in some patient characteristics between these two, non-randomised groups. For example, 88% of 'non-acceptors' (vs 36%) were married, 82% of 'acceptors' (vs 37%) were high school graduates, 63% of 'non-acceptors' (vs 27%) had experienced a decrease in ability to work at a job or do anything around the house and 38% of 'non-acceptors' (vs 18%) had experienced a decrease in ability to maintain a normal diet. These factors might contribute towards the patients' decision not to accept home treatment.

This paper presents little in the way of data but does report patients' feelings and experience. However, the patient group number is very low such that sub-group analysis is of little but anecdotal value.

Updated evidence (5.1)

Summary

An update search identified one paper on the topic of community versus hospital treatment.

One very limited, small RCT (Hall and Lloyd, 2008) reported outcomes on 15 women who all received at least four cycles of anthracycline-based chemotherapy, 5 women in hospital and 10 in their own home. All patients reported their experience by means of semi-structured interview. Women treated at home experienced feelings of comfort and safety, privacy and an appreciation of having extra time to use as they wished rather than travelling to hospital for their appointments. Home-treated women also reported developing a good relationship with the assigned treatment nurse whereas some hospital-based patients expressed dissatisfaction with the lack of continuity (receiving care from different nurses), the expense and inconvenience of travel and the stress of waiting, sometimes a long time in crowded clinics, to be seen. The advantages of hospital-based therapy included being able to meet others in similar situations to their own and, for some women, feeling safer in hospital in case anything went wrong with their treatment. None of the outcomes were quantified.

Reference

Hall M and Lloyd H (2008). Evaluating patients' experiences of home and hospital chemotherapy. *Cancer Nursing Practice* 7: 35-38

Evidence table

Question: Intravenous therapies in the community or as an in-patient?

Created by: Karen Francis on 12/06/2008

Hall and Lloyd (2008)
Design: RCT (other), evidence level: 1- Country: UK
Inclusion criteria: Women with breast cancer (stage unknown) in receipt of at least 4 cycles of anthracycline-based chemotherapy (suitability was determined by oncologist or breast care nurse). Written informed consent.
Exclusion criteria: None stated.
Population: Number of patients = 15, ages unknown.
Interventions: Patients were randomised to receive a minimum of 4 cycles of chemotherapy at home or in hospital. Individual semi-structured interviews were undertaken using a humanistic approach of phenomenology which focused on perceptions, attitudes, beliefs and values. The interviews were recorded and the resulting audio tapes transcribed. Data were then extracted following the principle of thematic analysis and were presented in narrative form.
Outcomes: Patient quality of life along four major themes: comfort & safety, privacy, practicality and relationships.
Follow up: N/A
Results: Comfort & safety: All home treated patients reported feeling comfortable and safe in their own home. However, some (not quantified) women also gained a feeling of safety by being in hospital 'in case something went wrong'. Privacy: Again, contrasting views were expressed. Being treated at home meant enjoying the feeling of privacy but, on the other hand, did not offer the opportunity to meet other people who were going through the same experience. Practicality: A number of patients (not quantified) highlighted the disadvantage of hospital visits on the basis of cost, time and anxiety. Women who weren't working sometimes found it expensive to travel to appointments and for those with young children the time factor was important. Being at home meant that patients could get on with their lives and distract themselves with tasks whilst waiting for the nurse to arrive rather than sitting in clinics being stressed and anxious. Relationships: Patients being treated in the home felt that having the nurse's 'full attention' gave them increased satisfaction in their care. The additional comfort of their home also meant that they were better able to concentrate and understand information given to them by the nurse, ask personal questions and establish a good relationship. Many women in the home received treatment by the same nurse every cycle whereas women in the hospital arm reported a lack of continuity in their nursing care.
General comments: This is a very limited trial of home versus hospital chemotherapy. All the data are qualitative and reported in narrative form. The absolute numbers of women reporting each outcome or opinion is not given other than in terms of 'some' or 'most' and the patient numbers are, in any event, very low.

The authors felt that the advantages to home therapy outweighed the disadvantages and the costs were reported as being the same. Several service issues were identified by all patients regardless of randomisation but these are not reproduced here.

Health Economic Summary

Although this topic was originally considered a priority for economic evaluation, the lack of clinical evidence meant it was not possible to make a recommendation. Therefore the economics were not investigated further.

Chapter 6 – Management of specific problems

6.1 Management of lymphoedema

Short summary

Fourteen papers addressed the topic of lymphoedema management comprising a guideline (Harris *et al.*, 2001) one very high quality systematic review (Moseley *et al.*, 2007) two systematic reviews of less quality (Kligman *et al.*, 2004 and Rinehart-Ayres *et al.*, 2007) four randomised trials (Didem *et al.*, 2005, Irdesel *et al.*, 2007, Badger *et al.*, 2004 and Johansson *et al.*, 2005) and five case series or phase II studies (Vignes *et al.*, 2007; Hamner and Fleming, 2007; Sitzia *et al.*, 2002, Kim *et al.*, 2007, Koul *et al.*, 2007 and Fiaschi *et al.* 1998). These papers all addressed lymphoedema management in women who had been treated for breast cancer but did not have active disease and, as such, the evidence only related to early breast cancer. The treatments evaluated included complex decongestive therapy (CDT), manual lymph drainage (MLD), pneumatic compression bandaging/garments, massage and exercise.

Intensive treatments, such as CDT and MLD, given by trained therapists and other health professionals, yielded better results than simpler maintenance treatments performed by the patient, carer or family member in the home. Patients given CDT experienced significant lymphoedema reduction and improvement in quality of life outcomes but an association between variables could not be proved definitively by a non-randomised study.

Pneumatic compression therapy was not significantly better at reducing limb volume when compared with no treatment, education or MLD but, when added to MLD, significantly improved oedema reduction and limb girth.

Multi-layer bandaging with hosiery was significantly better at reducing limb volume when compared with hosiery alone, an improvement still significant after six months.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with lymphoedema who have completed their primary cancer treatment and have no active disease	<ul style="list-style-type: none"> Simple lymph drainage Pneumatic compression therapy or pressotherapy Complex physical therapy (CPT), decongestive lymphatic therapy (DLT) or complex decongestive therapy (CDT) <p>(CPT, DLT and CDT describe intensive therapy comprising:</p>	<ul style="list-style-type: none"> No treatment Education only CPT/DLT/CDT <p>vs</p> <ul style="list-style-type: none"> Any single intervention or combination of the individual components All above compared to pressotherapy Simple lymph 	<ul style="list-style-type: none"> Reduction in swelling Containment of tissues- prevention of further oedema/life long control Softening of tissues Improvement in skin condition Improvement in function/mobility independence and activities of

POPULATION	INTERVENTION	COMPARISON	OUTCOME
	combinations of: <ul style="list-style-type: none"> • Manual lymphatic drainage (MLD) • Multi layer lymphoedema bandaging (MLLB) and/ or compression hosiery • Therapeutic exercise • Skin care and education 	drainage vs MLD	daily living <ul style="list-style-type: none"> • Pain reduced • Reduction in GP appointments, time off work, hospital admissions, related infections, depression / anxiety • Improved body image and QOL

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

All the papers included in this review addressed the management of lymphoedema in women who had received treatment for breast cancer but who did not, at the time of enrolment, have active disease. Such women were, in most cases, actively excluded from the particular studies. The principal outcome reported in most papers was the reduction of oedema in the affected limb. This parameter was assessed either by comparing before and after circumferential measurements in multiple sites along the arm and/or changes in limb volume, measured by water displacement. In all cases, absolute reduction was estimated with reference to the unaffected limb and therefore study participants were required to have unilateral lymphoedema only.

Studies that assessed all therapies

Note: some studies use the term 'complex or complete physical therapy' (CPT) and others 'complex decongestive therapy' (CDT). These interchangeable terms are reproduced in this summary as they are used in each paper.

The evidence includes two systematic reviews (Moseley *et al.*, 2007 and Kligman *et al.*, 2004) and a guideline (Harris *et al.*, 2001) which examined all standard lymphoedema treatments. Moseley *et al.* (2007) was a high quality review of combined studies (RCTs, parallel, crossover, case-control and cohort studies). The interventions comprised CPT, manual lymphatic drainage (MLD), simplified lymph drainage, pneumatic pumps, compression bandaging, compression garments and exercise. The outcomes of interest were the reduction in oedema after treatment and subjective symptoms rated by the study participants. Because the included studies were of various designs it was not possible to pool the data and so the authors summarised the findings in narrative form.

The authors found that CPT, either with or without pneumatic pump therapy, was an effective means of reducing oedema after a week to a month of application. The mean volume reduction across the included studies was ~25.5% and the reduction was maintained into the follow-up period, which was up to a year. Immediately after therapy the majority of participants reported an improvement in lymphoedema symptoms but this improvement was not assessed during follow-up.

MLD given alone was found to reduce oedema by up to 10%, an effect maintained for up to 6 months after application. When compared with self massage, MLD resulted in a significantly greater improvement in oedema reduction but when compared with a combined therapy of education, compression garment and exercise, MLD was not as effective in reducing limb volume although equal in improving patient rated subjective outcomes. When combined with compression or pump therapy, within 4 weeks MLD effected limb volume reductions of up to 84% but, unfortunately, a lack of follow-up meant that the authors couldn't comment on the likely long term benefits of treatment.

Limb volume reductions were also obtained from pneumatic pump therapy although one of the studies used rather high pressures (up to 150 mmHg) which might not ordinarily be approved. This treatment seemed to combine well with other forms of therapy such as MLD, compression or self massage. Compression garments or bandages appeared to make modest reductions in limb volume of up to 8% and reduced feelings of heaviness and tension reported by patients. Combining compression with exercise or self massage resulted in volume reductions of up to 60%. Modest improvements of lymphoedema volume, up to 9%, were obtained with exercise regimes and sometimes the positive effects lasted for up to 6 weeks after therapy.

The authors (Moseley *et al.*, 2007) concluded that the evidence suggested that the rather more intensive treatments, such as CPT and MLD given by trained therapists and other health professionals, yielded better results than the simpler maintenance treatments which could be performed by the patient or their carer or family member in the home. However, doing something with the affected limb was always preferable to doing nothing.

Kligman's review (Kligman *et al.*, 2004) was of RCTs only and included 5 such studies. Again, the heterogeneity between these studies, particularly in terms of intervention and outcome measurement, precluded pooling the data and hence the findings were summarised in narrative form. This review formed the basis for a Cancer Care Ontario summary of best available evidence which was used to formulate practice recommendations.

The addition of compression garments to self massage, assessed in one study, produced equivocal results over the long term due to a very high attrition rate but after 4 weeks of the combined therapy, recipients experienced a significantly greater oedema reduction than in the self-massage only (control) group.

A combined therapy including MLD, compression and exercise was compared with a similar regime without MLD but after 3 months there was no significant difference in lymphoedema response or in patient reported symptom improvement between the two study groups.

Pneumatic compression therapy was not significantly better at reducing limb volume when compared with no treatment or when compared with MLD nor did the latter trial detect significance in patient reported improvement of lymphoedema symptoms. Electrically stimulated lymph drainage (ESD) when added to compression therapy appeared to offer no significant advantage either in oedema reduction or symptom improvement.

From these five studies addressing physical (as opposed to medical) therapy, the authors concluded that more aggressive regimes were of no advantage compared with gentler treatment, thus contradicting the findings by Moseley *et al.* (2007). However, the comparatively low number of studies in this (Kligman *et al.*, 2004) review and their generally poor quality does not add weight to these conclusions.

Harris *et al.* (2001) is a Canadian lymphoedema guideline which looked at compression garments, pneumatic pumps and massage. The findings were presented in narrative form and may have been generated from papers of any type of study design or even from consensus. Hence the evidential value is considered low by comparison with, for example, a systematic review of RCTs. The recommendations which evolved from the available evidence were:

1. Practitioners may want to encourage long-term and consistent use of compression garments by women with lymphoedema.
2. One randomized trial has demonstrated a trend in favour of pneumatic compression pumps compared with no treatment. Further randomized trials are required to determine whether pneumatic compression provides additional benefit over compression garments alone.
3. Complex physical therapy, also called complex decongestive physiotherapy, requires further evaluation in randomized trials. In one randomized trial no difference in outcomes was detected between compression garments plus manual lymph drainage and compression garments alone.
4. Clinical experience supports encouraging patients to consider some practical advice regarding skin care, exercise and body weight.

Complex decongestive therapy (CDT)

Three papers (Vignes *et al.*, 2007, Hamner and Fleming, 2007 and Didem *et al.*, 2005) considered the effects of CDT on the reduction of lymphoedema volume and in Hamner and Fleming (2007) also the levels of pain and analgesia use.

Vignes *et al.* (2007) presented a high patient number, high quality prospective case series which has been graded as for a cohort study due to the strength of the analyses. In this trial, 537 women with secondary lymphoedema received CDT as in-patients for 11 days and then were followed for 1 year as they self treated with maintenance therapies. After 6 months and 1 year, just over half of the patients followed up experienced an increase in limb volume whilst the other half were either stable or had reduced limb volume. The maintenance therapy included the use of low stretch bandaging and wearing an elastic sleeve as well as exercise. The authors determined that in those patients whose lymphoedema increased by more than 10% over time, the greatest prognostic factors had been the non-compliance with either bandaging or wearing the sleeve. These factors were similar in impact and were independent of each other. Interestingly, the effect of MLD within the initial intensive hospital therapy was not significant on the eventual outcomes. The recommendations from this study were that after CDT women should be advised to wear elastic sleeves every day with bandages applied in the evening and worn through the night.

Hamner and Fleming (2007) presented a retrospective case series of modest evidential value. Patients receiving CDT were assessed before and after treatment but it was not clear from the results just how long the therapy had been given or at what point the follow-up assessment of limb volume had been made except that the average treatment period had been 14 weeks \pm 7 weeks. The 41.7% oedema reduction was significant ($P = 0.004$) as was the reduction in the pain scored by patients on a scale of 1-10 ($P < 0.001$).

Didem *et al.* (2005) described a small RCT comparing CDT with a standard physiotherapy (SP) regime (bandage, elevation, head, neck & shoulder exercises and skin care). Whilst data were not thoroughly reported, the resulting overall percentage reduction in lymphoedema was significantly different between CDT (55.7%) and SP (36%) ($P < 0.05$) after 4 weeks of therapy. Both groups gained greater shoulder mobility over time but neither treatment regime was preferable compared with the other in this respect.

Manual lymph drainage (MLD)

Two groups studied this therapy either with or without compression (Fiaschi *et al.*, 1998) or when compared to simple lymph drainage (SLD) (Sitzia *et al.*, 2002). Fiaschi *et al.* (1998) presented a very small ($n = 10$) and poorly reported case series of women with post-mastectomy lymphoedema in which participants were given MLD to which was later added the wearing of a compression bandage. It was found that the addition of compression to MLD significantly

improved oedema reduction and limb girth compared with MLD alone. Sitzia *et al.* (2002) presented a modest RCT of 28 patients who were randomised to receive MLD or a more simplified form of lymph drainage (SLD) which could have been applied by a non-specialist. However, both regimes were given every day for a fortnight on a hospital out-patient basis which may have been the reason for the low accrual and the subsequent unfortunate lack of power of the study. The mean reduction in limb excess volume with MLD was 33.8% compared with SLD 22% but with only 34% power to detect a significant difference between regimes the result is of reduced value.

Exercise and compression therapy

Two studies examined exercise with compression (Irdesel *et al.*, 2007 and Johansson *et al.*, 2005). Irdesel *et al.* (2007) randomised 21 lymphoedema patients to undergo a program of upper range-of-motion and light resistive exercises either wearing a compression garment or without. The primary outcome was reduction in limb size and volume and the follow-up period was 6 months. Limb size was measured at several points in the arm. After therapy, measurements at the wrist and distal to the epicondyle were significantly ($P = 0.03$ and $P = 0.05$ respectively) smaller in those patients on combined therapy, losses which were maintained after 3 and 6 months. For patients on exercise only, a significant improvement was only seen proximal to the epicondyle after 1 month ($P = 0.04$) but not beyond. One concern was that there appeared to have been baseline differences in wrist circumference which may well have skewed the results in favour of the control group but this was not mentioned by the authors and may have been of no statistical significance.

Johansson *et al.* (2005) presented a small ($n = 31$) trial of two exercise sessions with and without the concurrent use of a compression garment. Participants were randomised with regard to which of the two sessions they first wore the garment. The exercise program was repeated on 2 days with a day of rest between. The schedule involved weights, shoulder and elbow movements. Analysis showed that the order in which the compression garment was worn made no difference to the effects of exercise on lymphoedema volume. In contradiction to the findings by Irdesel *et al.* (2007), it was found that there was an immediate increase in limb volume after exercise, regardless of whether compression was being applied, but which declined after 24 hours (and was not assessed further). Since the authors felt that exercise was beneficial to the patients' overall wellbeing and had been assessed subjectively as 'light' by them, the lack of sustained limb volume increase led them to recommend the regime. However they did admit that this group of patients had only mild lymphoedema and that perhaps in those with more severe symptoms further assessments of the benefits of exercise should be undertaken. Unlike Irdesel *et al.* (2007) this study was not testing exercise with a view to reducing limb volume but rather was concerned only to determine if exercise would worsen the condition.

Multi-layer bandaging vs hosiery

Only one study (Badger *et al.*, 2004) made this comparison in people with unilateral lymphoedema (either primary or from cancer treatment). This study was included because the majority of participants were women and more people had an affected arm rather than leg. The multi-layer bandaging (MLB) consisted of inner tubular stockinette, foam and padding and an upper layer of short stretch bandages worn continuously for 18 days. This was followed by the use of hosiery which comprised a variety of items chosen for style and convenience and which was worn from morning to night for the duration of the trial (24 weeks). Participants were randomised to wear MLB then hosiery or to wear hosiery throughout. After 12 weeks, the reduction in limb volume in the MLB + hosiery group was about twice that seen in the hosiery only group (27.3% vs 12.1%) ($P < 0.001$) and this difference was maintained at week 24 (31% vs 15.8% ($P = 0.001$)). It is not certain that the trial participants had been treated for breast cancer and so these results must be viewed in this light but over 90% were women and over 60% had upper limb lymphoedema. Additionally, the author's discussion mainly centred round literature concerning lymphoedema secondary to breast cancer.

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Evidence tables

Question: Lymphoedema in breast cancer patients who have completed treatment and have no active disease

Created by: Karen Francis on 25/09/2007

Moseley <i>et al.</i> (2007)
Design: Systematic review of combined study designs (therapy), evidence level: 1+ Country: Australia
Inclusion criteria: Included studies: RCTs, parallel, crossover, case-control and cohort studies

<p>Included participants: Only women that had received a formal diagnosis of secondary arm lymphoedema subsequent to breast cancer surgery</p>																																																																
<p>Exclusion criteria: Excluded studies: Those which included women with recurrent breast cancer or primary lymphoedema</p>																																																																
<p>Population: Number of patients = not determined</p>																																																																
<p>Interventions: Complex physical therapy (CPT) Manual lymphatic drainage (MLD) Self/partner massage (simplified lymph drainage) Pneumatic pumps Compression bandaging Compression garments Limb exercises</p>																																																																
<p>Outcomes: Approximate oedema reduction expressed as a percentage loss between baseline and study end - calculated when this parameter was presented in studies as limb volume (ml). Subjective symptoms.</p>																																																																
<p>Follow up: N/A</p>																																																																
<p>Results: A table (6.1.1) summarising the narrative findings, is shown below.</p>																																																																
<table border="1"> <thead> <tr> <th>Therapy</th> <th>No. of studies</th> <th>% Reduction in limb volume at study end</th> <th>% Reduction at follow-up</th> <th>Symptoms reduced by end of study</th> </tr> </thead> <tbody> <tr> <td>CPT alone</td> <td>5</td> <td>18.7-66%</td> <td>yes in 3 studies no data</td> <td>pain, tightness, heaviness, cramps, pins & needles, tension</td> </tr> <tr> <td>CPT alone vs CPT + pump therapy</td> <td>1</td> <td>3.1% vs 7.9%</td> <td>3.6% vs 9.6% at 2mo</td> <td>yes – no details of which outcomes</td> </tr> <tr> <td>CPT alone + pump therapy</td> <td>2</td> <td>19.3-43.4%</td> <td>up to 40%</td> <td>-</td> </tr> <tr> <td>CPT regime including hand & mechanical massage, grip exercise, compression garment and hot compresses</td> <td>1</td> <td>8.5-13%</td> <td>-</td> <td>-</td> </tr> <tr> <td>MLD alone</td> <td>2</td> <td>8-10%</td> <td>maintained</td> <td>heaviness, tension</td> </tr> <tr> <td>MLD alone vs self massage</td> <td>1</td> <td>71 ml vs 30 ml (no % given)</td> <td>-</td> <td>heaviness, fullness, bursting</td> </tr> <tr> <td>MLD alone vs education, compression sleeve & limb exercise</td> <td>1</td> <td>48% vs 60% (nsd)</td> <td>66% (pooled data)</td> <td>heaviness, tightness (both groups) + discomfort (controls)</td> </tr> <tr> <td>MLD alone + compression bandaging</td> <td>2</td> <td>11-46.1%</td> <td>-</td> <td>tension, heaviness</td> </tr> <tr> <td>Compression sleeve then MLD alone</td> <td>1</td> <td>7% then 15%</td> <td>-</td> <td>tension, heaviness</td> </tr> <tr> <td>MLD alone + compression garment or bandage</td> <td>1</td> <td>84% or 78%</td> <td>-</td> <td>-</td> </tr> <tr> <td>MLD alone vs pneumatic pump + MLD</td> <td>1</td> <td>40% vs 45%</td> <td>increased by 33% if no further treatment</td> <td>-</td> </tr> </tbody> </table>					Therapy	No. of studies	% Reduction in limb volume at study end	% Reduction at follow-up	Symptoms reduced by end of study	CPT alone	5	18.7-66%	yes in 3 studies no data	pain, tightness, heaviness, cramps, pins & needles, tension	CPT alone vs CPT + pump therapy	1	3.1% vs 7.9%	3.6% vs 9.6% at 2mo	yes – no details of which outcomes	CPT alone + pump therapy	2	19.3-43.4%	up to 40%	-	CPT regime including hand & mechanical massage, grip exercise, compression garment and hot compresses	1	8.5-13%	-	-	MLD alone	2	8-10%	maintained	heaviness, tension	MLD alone vs self massage	1	71 ml vs 30 ml (no % given)	-	heaviness, fullness, bursting	MLD alone vs education, compression sleeve & limb exercise	1	48% vs 60% (nsd)	66% (pooled data)	heaviness, tightness (both groups) + discomfort (controls)	MLD alone + compression bandaging	2	11-46.1%	-	tension, heaviness	Compression sleeve then MLD alone	1	7% then 15%	-	tension, heaviness	MLD alone + compression garment or bandage	1	84% or 78%	-	-	MLD alone vs pneumatic pump + MLD	1	40% vs 45%	increased by 33% if no further treatment	-
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Pneumatic pump therapy + MLD alone	1	45% vs 45%	-	-
CPT + pump therapy vs CPT alone	1	45.3% vs 26%	CPT alone (only) maintained	-
Self massage, compression then pump therapy	1	3.3% then 9%	increase of 3.5% or additional reduction of 3%	-
Pneumatic pump therapy alone	1	7%	-	tension, heaviness
Compression garment then pump therapy (then compression garment)	1	17% overall	19.8% with continued use of compression	-
2-3h sequential pump therapy	1	12-44%	maintained if therapy continued 2h x 4pw	-
Compression bandaging	2	4-7%	-	tension, heaviness
Compression garment	2	5-8%	-	tension, heaviness
Compression garment + limb exercise	1	60%	-	-
Compression garment + self massage	1	24.4%	-	-
Arm exercise + deep breathing	1	5.8%	9%	tension, heaviness (maintained after 1mo)
Hydrotherapy	2	4.8%	2.9-8.6%	aching, heaviness, tightness, limb stiffness, swelling, heat intolerance
Hydrotherapy at 28°C or 34°C	1	12% decrease or 0.7% increase	-	unchanged for both
Deep breathing, self massage then limb exercises	1	12 ml (no %) after 20 min	-	range of movement, limb temperature difference, heaviness, tightness
Shoulder and elbow exercises with or without compression garment	1	increases of 0.5% or 0.3%	0.7-1%	unchanged for both
Back and arm exercises + weights with compression garment	1	2%	-	physical functioning, general health, vitality

Table 6.1.1 Lymphoedema reduction and subjective reporting of symptoms at study end and follow-up.

Complex physical therapy (CPT):

Five studies reviewed this intervention, some as a standalone treatment and others in combination with intermittent pump therapy. The treatment was given for between 8 days and 3 months. Not all papers were thorough in stating their inclusion and exclusion criteria. The range of follow-up was 1-12 months.

All the studies demonstrated that a reduction in limb volume and/or percentage of oedema could be achieved with CPT alone or in combination with other therapies. The optimal treatment time for CPT appears to be one month although 2/5 studies observed a volume reduction within 7-8 days. Volume reduction was continued into the follow-up period. 3/5 studies reporting subjective outcomes reported improvement after therapy but did not assess these outcomes at follow-up. The mean percentage volume change across studies was ~27.5%

Manual lymphatic drainage (MLD):

Two studies investigated the use of MLD alone and both were low patient number. Volume reduction was between 8-10% which was maintained, according to one of the studies, for 6 months after therapy. However, one of the studies did not state inclusion or exclusion criteria or state the length of treatment.

Two further studies made a comparison between MLD and a control therapy. The first (MLD vs self massage) found that after three weeks of therapy there was a statistically significant reduction in limb volume and improvements in subjective outcomes compared with a non-significant improvement with self massage. The second study (MLD vs education, compression garment and exercise) favoured the control group who experienced a greater reduction in limb volume (60%) compared with MLD (48%) and both groups reported improved subjective outcomes. Using pooled data the overall improvement in oedema was 66%, maintained at 12-months follow-up.

Four studies investigated the benefits of MLD when combined with compression (either bandage or garment). Reductions in limb volume ranged from 7-84% showing that either combination with MLD could be effectively used. Combination with pneumatic pump therapy was also effective. The majority of limb volume reductions were apparent after 4 weeks of treatment. Unfortunately, a lack of follow-up in these studies did not allow the authors to make strong conclusions about the long term benefits of MLD.

Pneumatic pumps:

Two studies showed that volume reductions could be achieved from pneumatic pump therapy alone although the pressures used in one of the studies (100-150 mmHg) exceeded that which would normally be recommended. Three studies demonstrated good results when pump therapy was combined with other treatments (MLD, compression garments or self massage) and three different studies showed that initial benefits could be obtained by continuing to wear a compression or undergoing further pump therapy.

Compression:

Four studies showed that modest reductions of between 4-8% and significant improvement in subjective symptoms such as heaviness and tension could be obtained when using compression (bandaging or garment) alone. Since none of the included studies had a follow-up period, the absolute value of this therapy could not be determined. Combining compression with exercise or self massage resulted in volume reductions of up to 60%.

Limb exercises:

Five studies demonstrated that exercise have differential effects on limb volume. Results varied from 0.4-9% with improvement in symptoms. In some cases the improvements were maintained during follow-up of between 2 hours and six weeks after cessation. Hydrotherapy should be undertaken at a temperature of 28°C.

General comments:

This was a concise and very thorough systematic review of mixed design studies which considered common conservative interventions for the treatment of secondary lymphoedema after breast cancer surgery. Twenty-six reviewed studies were relevant to the outcomes of interest.

The review methodology was well documented and the literature search was conducted from fourteen databases including Medline, Cinahl, CANCELIT and the Cochrane Library. All included studies were graded for quality.

Due to the heterogeneity of the included studies the authors could not perform a meta-analysis but instead gave a narrative synthesis of the findings.

The authors concluded that intensive treatments administered by trained health professionals (including CPT and MLD) generally yielded a larger percentage of limb volume reductions than maintenance therapies undertaken by the patient (compression garments, exercise etc) but that the latter were preferable when compared with doing nothing at all with the affected limb.

Kligman <i>et al.</i> (2004)
Design: Systematic review of RCTs (therapy), evidence level: 1- Country: Canada (federal state, Commonwealth Realm)
Inclusion criteria: Included studies: Randomised trials or systematic reviews of randomised trials of treatment for lymphoedema related to the treatment of breast cancer that measured the effect of therapy on arm volume, symptom control, quality of life or cosmetic results.
Exclusion criteria: Non-English language reports
Population: Number of patients = 239
Interventions: Compression garments, manual lymphatic drainage (MLD), education, exercise, pneumatic compression pumps, electrically stimulated lymphatic drainage
Outcomes: Primary outcome: Proportion of patients with a reduction in lymphoedema Secondary outcomes: Difference in arm volume between the patient's control and treated arm, reduction in lymphoedema symptoms, Quality of life, adverse effects of treatment
Follow up: Variable
Results: The total number of participants in the five included studies was 239. Compression garments + self massage vs self massage only: Hornsby <i>et al.</i> (1995) presented a study on elastic compression sleeves that were fitted to women attending a lymphoedema clinic. Participants were asked to wear the sleeves day and night. Both intervention and control patients were taught self massage techniques and exercises by a physiotherapist. The study was designed to run for one year but by 16 weeks all the control group and half the experimental group had dropped out. At the first assessment (week 4) 12/14 women in the intervention arm and 4/11 women in the control arm had exhibited reduced swelling. MLD + self massage + compression garment, education and exercise vs compression garment, education and exercise: Anderson <i>et al.</i> (2001) compared these regimes on women attending a lymphoedema clinic. The duration of compression treatment was not specified but the MLD was performed over a one-hour period 8 times in a two week period. Lymphoedema (mean percentage reduction) was measured at baseline and after 1 and 3 months and comparison made between the affected and unaffected limbs. 10 control group members crossed over to MLD therapy after 3 months and all participants were followed up for a further 9 months from that point. Pneumatic compression pumps vs no treatment: Dini <i>et al.</i> (1998) randomised women with post-surgical lymphoedema to receive constant pressure (60 mmHg) pneumatic therapy for a 2 hour session repeated 5 times weekly or no treatment. This cycle was repeated after a 5 week break. No other physical therapy was allowed during this 9 week period. Pneumatic compression pumps vs MLD: Johansson <i>et al.</i> (1998) compared pneumatic compression with MLD. Nine compression cells

applied 40-60 mmHG in a 2 hour session which was administered 5 days a week for 2 weeks. Participants were directed to wear a compression sleeve for 2 weeks before randomisation and during the day for the duration of the trial.

Electrically stimulated lymph drainage (ESD) + compression garment vs compression garment only:

Bertelli *et al.* (1991) made this comparison in patients who first had to wear a standard elastic sleeve for 6 hours per day before the treatment allocation. ESD was used as induction therapy in the intervention group and was applied at 4.5kHz for 30 minutes in 2 cycles of 10 sessions over 2 weeks. After a break of 5 weeks, the regime was repeated. No other treatment for lymphoedema was permitted during the trial.

The results are summarised below in table 8.1.2:

Trial	Intervention	Response rate* n (%)	Mean reduction in arm volume from baseline	Improvement of symptoms
Hornsby <i>et al.</i> , 1995	Compression sleeve plus exercise/massage Exercise & self-massage	12 (86%) P = 0.042** 4 (36%)	Not reported	Not reported
Andersen <i>et al.</i> , 2000	MLD plus self massage plus standard therapy Standard therapy: compression garment, education, exercise	Not reported	48% (95%CI: 32-65) 60% (95% CI: 43-78) nsd	No significant difference between groups
Dini <i>et al.</i> , 1998	Intermittent pneumatic compression No treatment	10 (25%) 8 (20%)	1.9 (± 3.7) cm 0.5 (± 3.3) cm nsd	Not reported
Johansson <i>et al.</i> , 1998	Sequential pneumatic compression MLD	Not reported	28 ml 75 ml P = 0.11	No significant difference between groups
Bertelli <i>et al.</i> , 1991	Electrically stimulated lymphatic drainage Elastic sleeve	13 (38%) 10 (29%)	"About 17% in both groups"	Not reported

Table 6.1.2: Abbreviations: MLD manual lymphatic drainage, SD standard deviation.

* Response rate: patients with reduction in swelling

** Review author's calculation using Fisher's exact test (1-tailed)

*** Reduction in difference between normal and affected arm

General comments:

This document is an evidence summary report, which is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline.

The report was reviewed by the Supportive Care Guidelines Group, which includes palliative care physicians, nurses, radiation oncologists, psychologists, medical oncologists, a chaplain, an anaesthetist, a surgeon, methodologists, and administrators. The report was also externally reviewed by Ontario practitioners (via a mailed survey).

Evidence for the review was searched from MEDLINE (May 2000 to March 2002), CANCERLIT (May 2000 to March 2002), HealthStar, CINAHL, PREMEDLINE and Cochrane Library databases as an update to a practice guideline published in 2001 (Harris SR, Hugi MR, Olivotto IA, Levine M, for the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 11. Lymphedema CMAJ 2001;164:191-9).

Pooling data from the selected studies was not undertaken because the authors felt that physical and medical therapies should be separately reviewed. No two trials examined the same physical

therapy intervention. The evidence was therefore presented in narrative form.

The evidence in this summary was obtained from 10 RCTs. Five of these trials (Hornsby *et al.*, 1995, Anderson *et al.*, 2000, Dini *et al.*, 1998, Johansson *et al.*, 1998 and Bertelli *et al.*, 1991) related to therapies of interest and all of but one of these (Hornsby *et al.*, 1995) were reviewed in the earlier practice guideline (Harris *et al.*, 2001). The other five RCTs dealt with medical interventions for the treatment of lymphoedema (e.g. coumarin, benzopyrones and Daflon) or were concerned with lymphoedema prevention rather than treatment.

2/4 trials examining physical therapies used a control group who received no intervention and the other control groups received active treatment. These studies usually only conducted therapy trials for short periods (2 weeks - 2 months). None of the trials used blinded outcome assessments.

4 trials measured arm volume using water-tank submersion. The remaining 6 trials estimated arm volume by taking limb-circumference measurements at a number of sites (between five and eight). The amount of oedema was determined by calculating the difference in volume between the oedematous and normal arm.

None of the included studies reported on quality of life or adverse effects.

From RCTs of physical therapy for lymphoedema the only positive finding was an incremental benefit when use of an elastic sleeve was added to self-massage therapy. Pneumatic compression (compared with no intervention) was not associated with a significant improvement of the magnitude that the study was powered to detect but the direction of the response rates and changes in arm volume favoured pneumatic compression. None of the other, more aggressive approaches were found to have benefits when compared with less aggressive controls. The heterogeneous outcomes used to measure treatment effects make synthesising the evidence difficult.

Fiaschi <i>et al.</i> (1998)
Design: Case series (therapy), evidence level: 3 Country: Italy
Inclusion criteria: Women with post-mastectomy (for breast cancer) lymphoedema
Exclusion criteria: None stated
Population: Number of patients = 10 age range = 40 to 70 years
Interventions: Manual lymphatic drainage (MLD) first without then with compression bandage. MLD was conducted for 1 hour per session and for 10 sessions.
Outcomes: Circumferential measurements of affected limb before and after therapy (absolute reduction). Volume reductions of affected limb using the unaffected limb as a control value (percentage decrease).
Follow up: N/A
Results: Mean absolute reduction of circumference in cm after MLD (n = 10):

<p>Whole limb = 1.4 ± 0.1</p> <p>Mean absolute reduction of circumference in cm after MLD with compression bandage: Whole limb = 1.4 ± 0.6</p> <p>Mean absolute reduction of circumference in cm after MLD without compression bandage: Whole limb = 0.9 ± 0.1</p> <p>Mean total percentage decrease in limb volume after MLD: Whole limb = 35.7 ± 11.3</p> <p>Mean total percentage decrease in limb volume after MLD with compression bandage: Whole limb = 41.1 ± 12.2 ($P < 0.05$)</p> <p>Mean total percentage decrease in limb volume after MLD without compression bandage: Whole limb = 30.4 ± 15.8 ($P < 0.05$)</p>
<p>General comments: This is a very small, poorly reported case series on ten women with chronic lymphoedema following treatment for breast cancer. No other patient characteristics were given and so the clinical condition of these participants is unknown. There were no comparators to the intervention. The authors suggest that the addition of compression therapy following MDT leads to significant reductions in both limb girth and absolute volume. There was no follow-up.</p> <p>The grade of lymphoedema was assessed using an oedemometer.</p>

<p>Badger <i>et al.</i> (2004)</p>
<p>Design: Randomised controlled trial (therapy), evidence level: Country: UK</p>
<p>Inclusion criteria: Lymphoedema as a result of treatment for cancer or primary lymphoedema (diagnosed by lymphoscintigraphy) Cancer patients had to be at least 12 month disease-free At least 20% excess volume in the affected limb Unilateral limb involvement Written consent</p>
<p>Exclusion criteria: Patients with bilateral lymphoedema Paralysis History of compromised arterial flow in the affected limb Patients too big to wear the hosiery</p>
<p>Population: Number of patients = 83, males = 7, females 76, mean age = 57, age range = 23-86 years</p>
<p>Interventions: Multi-layer bandaging (MLB) worn on day 1 and continued for 18 days followed by hosiery for the remainder of the trial (MLB + H) vs hosiery alone (H) for the entire trial (24 weeks).</p> <p>The MLB consisted of a length of tubular stockinette with retention bandaging to digits and joint protection with foam and padding such that even pressure was applied throughout. The final layer was short stretch, extensible bandages. The dressings were changed once daily and worn continuously.</p>

The hosiery consisted of a variety of items chosen for style, class of compression and number of layers according to requirement. These garments were worn from morning until night and changed every three to four months.

All patients were also given advice on positioning the affected limb, exercises to promote lymph drainage, self-massage and daily skin care. Patients were asked to perform exercises and attend to skin care and massage every day for the duration of the trial.

Outcomes:

Reductions in the volume of an upper or lower limb affected with lymphoedema. The primary outcomes were percentage reduction at week 24 and average volume reduction over the course of the study.

Follow up:

Baseline assessments of limb volume and adverse events were made on day 1, day 19, week 12 and week 24.

Originally 90 patients were enrolled but 7 patients were withdrawn (4 from MLB + H) for various reasons including patient choice, failure to receive all treatments and disease recurrence. During the study there were 8 cases of cellulites (5 from MLB + H), 1 case of DVT and 3 patients with disease recurrence (2 from MLB + H).

Results:

The reduction in limb volume in the MLB + H group was approximately twice that seen in the H group:

Day 1 to week 12:

MLB + H (n = 32) mean percentage reduction = 27.3

H (n = 46) mean percentage reduction = 12.1 (P < 0.001)

Day 1 to week 24:

MLB + H (n = 32) mean percentage reduction = 31.0

H (n = 46) mean percentage reduction = 15.8 (P = 0.001)

Similar results were obtained when reductions over time were calculated:

Day 19:

MLB + H (n = 34) = 33.5 ± 16.9

H (n = 47) = 9.6 ± 20.4

Week 7:

MLB + H (n = 33) = 26.0 ± 21.0

H (n = 45) = 13.8 ± 21.6

Week 12:

MLB + H (n = 32) = 34.5 ± 20.7

H (n = 45) = 18.0 ± 23.0

Week 24:

MLB + H (n = 32) = 32.6 ± 33.2

H (n = 46) = 19.6 ± 28.5

The authors conclude that the beneficial effects of MLB + H were long-lasting, being apparent after 12 and 24 weeks.

General comments:

This moderate quality paper describes a parallel group RCT of participants of both genders and with upper or lower limb lymphoedema secondary to treatment for cancer at the Royal Marsden Hospital in London. The majority of participants were women (91% intervention groups and 92%

control group) and the majority of participants had an upper limb affected (62% intervention and 67% control). Although the details of specific cancers are not detailed in the patient characteristics, the discussion focuses predominantly on breast cancer and so it maybe that the majority of participants in this study were treated for this disease. Participants were randomised by telephone through an epidemiology centre.

Limb volumes were assessed by an electronic volumeter. Severity of swelling was determined by reference to the unaffected (control) limb and expressed as a percentage thereof.

Vignes *et al.* (2007)

Design: Prospective case series (therapy), evidence level: 2+
Country: France

Inclusion criteria:
Women referred with upper limb lymphoedema secondary to treatment for breast cancer

Exclusion criteria:
Past history of attempted lymphoedema treatment by any means

Population:
Number of patients = 537, Females = 537, Median age = 62 years, range = 34-91 years

Interventions:
The programme consisted of an 11-day hospitalisation (intensive phase) of CDT followed by maintenance therapy undertaken by the patient and family at home. During the hospital phase, patients and family members were given instruction on bandaging techniques and skin care.

Complete (complex) decongestive therapy (CDT): Manual lymphatic drainage (30 minutes), low stretch compressive bandage wrapped in 2-4 layers over foam covering (worn for 24 hours daily) with exercise and elastic sleeve.

The first day of hospitalisation was considered day 1 of the study.

Outcomes:
Lymphoedema volume before and after CDT.

Follow up:
Baseline data collection included breast cancer staging and treatment, BMI and lymphoedema volume. The latter was calculated for each 5cm segment of the limb utilising a formula for measurement of a truncated cone. Measurements of limb volume were made by the same operator at study inclusion, after CDT and at 6 and 12 months. Details of maintenance therapy undertaken at home were recorded.

Missing data resulted in 2 women being excluded from the final analysis. During the one-year follow-up phase 24 (4%) participants died from causes not detailed.

Results:
Lymphoedema volume prior to intensive CDT = 1054 ± 633ml
Lymphoedema volume following intensive CDT = 647 ± 351ml (P < 0.0001)
Mean absolute volume reduction = 407ml (95%CI: -440 to -374 ml)

Foam padding was used in 70% of patients and cotton in the other 30%. At discharge, 86% patients were fitted with class 3 elastic sleeves (20-36 mmHg) and 14% were given class 2 (15-19 mmHg).

After 6 months (n = 426):
Mean increase in lymphoedema volume = 78 ml

Number of patients whose volume increased by > 10% = 217 (51%)
 Number of patients whose volume was stable = 85 (20%)
 Number of patients whose volume decreased = 124 (29%)

After 12 months (n = 356):

Mean increase in lymphoedema volume compared with volume after CDT = 84 ml
 Mean increase in lymphoedema volume compared with volume after 6 months = 22 ml
 Number of patients whose volume increased by >10% compared with volume after CDT = 186 (52%)

Number of patients whose volume was stable \pm 10% compared with volume after CDT = 71 (20%)

Number of patients whose volume decreased compared with volume after CDT = 124 (28%)

During the maintenance phase, the risk of increase in limb volume due to lymphoedema of > 10% was more than 50% likely in those women not using a low stretch bandage (RR = 1.55, 95%CI: 1.3-1.76 P < 0.0001) or elastic sleeve (RR = 1.61 95%CI: 1.25-1.81 P = 0.002) – these factors were independent of each other. In contrast, the risk was unchanged whether or not people used MLD during this phase.

General comments:

This prospective cohort study followed 537 women for a one year maintenance period following CDT. Lymphoedema volume was measured before and after CDT and at 6 and 12 months. Each of the three components of therapy were separately evaluated. Participants were recruited between January 2001 and December 2004 at a single centre. The attrition rates were 21% after 6 months and 33% after one year which are acceptable.

The authors felt that this study design ensured as much as possible that heterogeneity had been minimised such that the results were more likely to be attributable to the interventions. However, they also pointed out that participants were not randomly allocated and hence the observed treatment effects may have been due to some unidentified confounding factors.

Recommendations from this study were that during the maintenance phase, after decongestive physiotherapy, patients should be advised to wear elastic sleeves every day with self bandages applied in the evening and worn throughout the night. A frequency of three bandages per week was believed to be optimal.

Didem *et al.* (2005)

Design: Randomized controlled trial (therapy), evidence level: 1-
Country: Turkey

Inclusion criteria:

Women with mild (increased limb circumference of up to 2 cm) to moderate (increased limb circumference of 2-5 cm) lymphoedema
 Lymphoedema for at least 1 year

Exclusion criteria:

Obvious ongoing psychiatric illness
 Severe pain in the axillary region
 Severe cardiac disease
 Uncontrolled hypertension (> 160/95)
 Malignant disease

Population:

Number of patients = 53, age range 31 to 76 years, mean age = 58 years

Interventions:

Patients were randomised to one of the following regimes and taken to the treatment centre once

a day, 3 days a week for 4 weeks:

1] Complex decongestive therapy (CDT) (n = 27): lymph drainage, multi-layer compression bandage, elevation, remedial exercises and skin care.

2] Standard physiotherapy (SP) (n = 26): bandage, elevation, head-neck & shoulder exercises and skin care.

A home program of bandage, skin care and walking was also recommended to all patients.

Outcomes:

Reduction of lymphoedema (in terms of circumference and volume), shoulder mobility.

Follow up:

Baseline assessments included a complete medical history and circumferential measurements of both affected and non-affected limbs. Arms were measured at eight points: 15, 15 and 20 cm above and below the elbow, at the wrist and in the hand. Limb volume was measured by water displacement. Shoulder mobility was also measured.

Follow-up assessments of these factors were made after treatment was concluded (4 weeks). Long term follow-up was not reported in this paper.

Results:

60.4% patients had moderate and 39.6% mild lymphoedema at baseline. The mean baseline limb volume was 580 ml and the mean duration of lymphoedema was 3.4 years across all patients.

Overall mean reduction in oedema after treatment (4 weeks):

CDP = 55.7%

SP = 36% (P < 0.05)

NB. Patient data for this outcome was reported for only one group but is not labelled with the identity of that group.

Reduction in range of motion in shoulder before treatment:

CDP = 48.1%

SP = 42.3%

Shoulder flexion and abduction were significantly increased in both groups (P < 0.05) but there was no improvement in external rotation. There was no significant difference between treatment groups in improved mobility.

General comments:

This paper presents a small RCT of women with unilateral lymphoedema secondary to breast cancer treatment. Participants were randomised by means of cards in unmarked envelopes to receive either CDT or standard physiotherapy regimes.

The data reporting is minimal and incomplete for both treatment groups. CDP appears to have made a significantly greater impact on lymphoedema reduction than the standard physiotherapy regime. Shoulder movement improved for all patients but there was no difference between treatment groups.

Irdesel *et al.* (2007)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: Turkey

Inclusion criteria:

Informed consent

<p>Exclusion criteria: Surgery less than 4 months before study entry Disease recurrence or active disease, stage IV cancer Bilateral breast cancer Elephantiasis, congestive heart failure, acute DVT, acute or untreated infections in the target limb</p>
<p>Population: Number of patients = 21, age range 33 to 64 years, mean age = 52 years</p>
<p>Interventions: Patients were randomised to receive:</p> <p>1] An exercise treatment program - upper extremity range-of-motion exercise and light resistive exercise. The routines were explained and demonstrated to patients.</p> <p>2] The same exercise treatment program with compression garment - this applied 40mmHg pressure - participants were asked to keep this garment on at all times except when sleeping. Garment use was maintained for 6 months.</p> <p>All patients were informed and given booklets about appropriate skin care and also some lifestyle suggestions to prevent progressions of lymphoedema.</p>
<p>Outcomes: Difference (from baseline) in limb size calculated from circumferential measurements of the arm taken at 4 sites (carpometacarpal joint, wrist, 15 cm proximal and 10 cm distal to the lateral epicondyle) and at the same time of day on each occasion.</p> <p>Improvement in the range of shoulder movement, measured with a goniometer.</p> <p>Symptoms related to lymphoedema e.g. pain (measured on a visual analogue scale. Shoulder tenderness was recorded on a scale of 0-3.</p>
<p>Follow up: Patient characteristics were obtained together with an assessment of the size and range of shoulder movement in the affected limb. Limb measurements were repeated at the 2nd week, 1 month, 3 months and 6 months.</p> <p>Follow-up was for at least six months.</p> <p>Two patients (one in each group) failed to complete the study, one because of DVT (exercise group) and one due to lymphangitis.</p>
<p>Results: All patients had received prior radiotherapy and surgery for breast cancer.</p> <p>Since only 1 patient at baseline had reported pain and tenderness therefore this parameter could not be compared statistically between the two groups. A similar finding applied to restricted shoulder movement.</p> <p>Circumferential limb measurements: Baseline vs 2nd week - group (1): carpometacarpal joint = 0.6 ± 0.6 vs 0.5 ± 0.37 wrist = 0.7 ± 0.71 vs 0.8 ± 0.55 10 cm distal = 2.3 ± 1.90 vs 2.0 ± 2.32 15 cm proximal = 3.4 ± 1.38 vs 3.2 ± 1.23</p> <p>Baseline vs 2nd week - group (2): carpometacarpal joint = 0.6 ± 0.4 vs 0.4 ± 0.27</p>

wrist = 1.4 ± 0.77 vs 0.9 ± 0.31
 10 cm distal = 3.3 ± 1.75 vs 2.7 ± 1.27
 15 cm proximal = 2.5 ± 1.48 vs 2.7 ± 1.19

Group (2) showed a statistically significant improvement in wrist ($P = 0.032$) and distal ($P = 0.05$) measurements between baseline and week 2 but not in the carpometacarpal joint or proximal measurements. The reduction in wrist measurement for this group continued to be significant after 1 month ($P = 0.046$), 3 months ($P = 0.009$) and 6 months ($P = 0.008$). The reduction in distal circumference was also significant after 3 months ($P = 0.005$) and 6 months ($P = 0.05$).

For group (1) a single improvement in proximal circumference was measured at 1 month ($P = 0.043$).

There were no statistically significant differences between the groups concerning the comparison of the baseline and follow-up circumferential measurements at all measurement sites ($P > 0.05$).

General comments:

This paper describes a small ($n = 19$) RCT comparing exercise with the use of compression garments in the treatment of unilateral upper limb lymphoedema secondary to breast cancer therapy.

Patients were randomised into the two groups by 'another researcher' who may or may not have been involved with this particular study. Assessments were made by a researcher blinded to treatment allocation (presumably, although it is not stated, those patients randomised to wear a compression garment at all times would have had to remove the garment before these assessments).

A graph of wrist measurements for both groups throughout the study suggest that there may have been a significant difference in baseline values between group (1) and group (2) (0.7 ± 0.71 vs 1.4 ± 0.77 respectively) but no statistics were offered with regard to comparison of baseline values between the groups other than those relating to diagnosis, tumour staging etc. No reason was given for failing to present these data.

Sitzia *et al.* (2002)

Design: Randomized controlled trial (therapy), evidence level: 1-
Country: United Kingdom

Inclusion criteria:

Women over the age of 18 years with unilateral lymphoedema secondary to treatment for breast cancer
 Previous treatment for breast cancer to have included surgery or radiotherapy to the axilla and/or breast
 No known active disease
 Minimum baseline limb volume excess of $\geq 20\%$
 No previous treatment for lymphoedema (except hosiery).

Exclusion criteria:

None stated

Population:

Number of patients = 28, age range 48 to 91 years, mean age = 71 years

Interventions:

Patients were randomised to either

1] Manual lymph drainage (MLD) ($n = 15$) defined as a type of skin massage undertaken by a

trained therapist designed to increase lymph flow and reabsorption without increasing filtration. The same therapist treated all patients.

2] Simple lymph drainage (SLD) (n = 13) defined as a less complex technique than MLD which could be applied by a therapist or by the patient/carer with no specialist training.

Both treatments were given daily (on weekdays) at a hospital out-patient department for two consecutive weeks. The lymph drainage therapy was followed by a sequence of bandaging and exercises by all patients.

Outcomes:

Change in the percentage of excess volume.

Follow up:

Assessments were made at baseline and after the two week trial. After the final assessment, participants were initiated into a standard treatment regime at the hospital but did not participate further in the trial.

Results:

Data was recorded from 27 patients (one patient withdrew after 5 days) of which 25 patients were assessed for the outcome:

The MLD therapy group experienced a mean volume reduction of 33.8% (SD = 21.2 range: 2.4-79.7). 1 patient had an increase of 2.4%.

The SLD therapy group experienced a mean volume reduction of 22% (SD = 17.3 range: 2.4-44.6. 1 patient had an increase of 2.4%.

The mean difference between groups was 11.8% (95%CI: -3.8-27.4) (nsd). As the power of this study was only 34% (due to the low participant number) this is significantly underpowered to draw conclusions from the result. These data could be used to determine the appropriate participant number in a full scale trial (for 90% power this would be approx. 47 participants per group to achieve the same result as this pilot study and more if the anticipated mean difference between treatments was believed to be higher than ~12%).

General comments:

This paper presents the results of a small (n = 28) RCT which compares manual (MLD) versus simple (SLD) lymph drainage in the treatment of unilateral arm lymphoedema secondary to breast cancer therapy.

The pilot study accrued rather a low number of patients, possibly because the inclusion criteria were strict and the therapy involved participants attending every day at hospital. Recruitment was open from January 1996 to June 1999.

Randomisation was by means of a computer generated code and results data were managed by an independent, non-clinical researcher.

Limb volume was calculated using circumferential arm measurements at eleven set points. The limb volume change was determined from an equation comparing before and after therapy measurements and those between affected and unaffected limbs.

The authors feel that MD is the more effective therapy but, with a very underpowered study, this conclusion has yet to be demonstrated with significance.

Hamner and Fleming (2007)

<p>Design: Retrospective case series (therapy), evidence level: 3 Country: United States</p>
<p>Inclusion criteria: None stated</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 135, age range 23 to 92 years, mean age = 54 years</p>
<p>Interventions: All patients received a standard protocol of complete decongestive therapy (CDT) comprising: manual lymphatic drainage (MLD), skin care, compression bandages and exercise.</p> <p>MLD was given twice a week and patients wore elastic compression garments (changed twice daily) between these sessions. Participants were also instructed on skin and nail care and given a personalised exercise program to facilitate lymph flow and improve range of motion for the affected limb.</p>
<p>Outcomes: A comparison of before and after treatment limb volume determined by water displacement, patient subjective assessment of levels of chronic pain (10-point scale) and their need for analgesia.</p>
<p>Follow up: Limb volume assessments were made before and after patients received CDT.</p>
<p>Results: 119/135 women received this protocol of which 119 had unilateral (as opposed to bilateral) lymphoedema as a result of breast cancer treatment.</p> <p>The average number of treatments per patient was 14.3 ± 6.8 and the average number of weeks that CDT was received was 7.5 ± 3.4. The variability between patients is unknown but is assumed to be fairly large.</p> <p>Mean lymphoedema volume before therapy = $709\text{ml} \pm 76\text{ ml}$ Mean lymphoedema volume after therapy = $473.2 \pm 48.9\text{ ml}$ ($P = 0.004$). Percentage reduction in lymphoedema volume = 41.7%.</p> <p>Mean score of pain perception before CDT ($n = 76$) = $6.9 (\pm 2.3)$ on a scale of 0-10. Mean score after CDT = $1.1 (\pm 2.3)$ ($P < 0.001$)</p> <p>56/76 (76%) patients who had experienced pain before CDT became pain-free after treatment. Of the 76 patients who had pain, 41 required analgesia before CDT but this was reduced to 11% after completing the CDT protocol. 1 patient reported increased pain and 2 previously pain-free patients experienced pain after CDT.</p>
<p>General comments: This low quality evidence describes a retrospective study of case files from patients at a lymphoedema clinic who had been treated using a standard protocol of CDT. There was no comparator.</p> <p>The participants had severe oedema (mean of 31%) which was significantly reduced by CDT. Pain was also significantly reduced, either from the CDT or from a placebo effect of the constant hands-on therapy.</p> <p>Unfortunately, there is no time frame within which to assess the results since it is not obvious</p>

from the data when the follow-up lymphoedema measurements were obtained i.e. after one session or several, and the actual number of sessions per patient is unknown.

The presentation of data does not help an assessment of the variability in results over the entire patient group and hence the conclusions of efficacy must be viewed with great caution.

Patient compliance and motivation were also assessed but no results were reported.

Harris *et al.* (2001)

Design: Guideline (therapy), evidence level: 4

Country: Canada (federal state, Commonwealth Realm)

Inclusion criteria:

-

Exclusion criteria:

-

Population:

Number of patients = not reported

Interventions:

Compression garments, pneumatic compression pumps, massage and physical therapies. Other treatments were considered but are not included here.

Outcomes:

To provide information and recommendations for women and their physicians when making decisions about the management of lymphoedema related to breast cancer.

Follow up:

-

Results:

Note that the review results were presented in narrative form and derived from a mixture of RCTs, other sources and what may be consensus statements. The findings are summarised with source, where known.

Compression garments:

- . Graded compression garments that deliver 20-60 mmHg pressure may be used as primary therapy
- . Opinions are divided over the duration of use from constant to only during waking hours or when exercising
- . Compression garments may protect against burns and bites etc.
- . Mean significant decreases of 9% (proximal) and 26% (distal) have resulted from the use of compression garments (RCT)
- . Compression sleeve with or without electrically stimulated lymph drainage reduced limb girth equally (17%) (RCT)
- . Good compression garments may be custom-made or prefabricated, should be fitted by trained personnel and replaced every 4-5 months or when they lose elasticity
- . Patients may be non-compliant in wearing what to them is unsightly, uncomfortable, difficult to put on and expensive
- . Customised, lightweight and colourful garments may provide options for comfort and wear.

Pneumatic compression pumps:

- . Post-mastectomy lymphoedema was either untreated or exposed to five two-hour pneumatic pump therapy sessions. There was no significant difference in circumferential arm measurement between groups after two weeks (RCT). Low patient numbers in this trial may have skewed the

results.

- . Pneumatic compression produced an 18% higher reduction in lymphoedema volume than elastic compression (two studies)
- . There were no comparative studies by which the most effective pumping time, pressure levels or make of pump could be determined
- . There was some (not unanimous) agreement that sequential, multi-chambered pumps were more effective than mono-chambered pumps
- . Pump therapy is contraindicated when active infection or DVT is present.

Massage and physical therapies:

- . There was no significant difference in either objective measure of limb volume or subjective measure of symptoms relief between two groups of study participants. One group received standard therapy (compression garment worn during the day, instruction in physical exercises, education in skin care and information) and the other group received standard care plus manual lymph drainage and self-massage training (RCT)
- . In a study comparing compression bandaging with or without manual lymph drainage the combined treatment resulted in a significantly greater reduction in limb volume but symptom relief did not differ between groups. (cohort study)
- . Some case series reported alleviation of lymphoedema with massage and other physical therapies
- . In one study, manual lymph drainage plus sequential pneumatic compression was assessed with or without the use of a compression garment but no difference was found between groups in the response.
- . The efficacy of six months of compression garment use was not improved by the addition of electrically stimulated lymphatic drainage or pneumatic pump therapy.

Pain reduction:

- . Pain and discomfort can best be addressed by controlling the lymphoedema.
- . Refractory pain can be managed with narcotic and non-narcotic analgesics and, where necessary tricyclic anti-depressants, corticosteroids, anticonvulsants or local anaesthetics
- . Aggravating conditions such as infection and cancer recurrence should be promptly treated.

Psychosocial issues:

- . Such issues should be promptly recognised and addressed
- . Women with lymphoedema have been shown to have a greater psychiatric morbidity and functional disability.

Practical advice about skin care, exercise and body weight:

- . Scrupulous skin care should be encouraged and, wherever possible, women should avoid all medical interventions to the affected limb e.g. vaccination, blood sampling
- . Women with lymphoedema should avoid saunas, hot baths or extended travel in hot climates.
- . Compression garments should be worn whilst flying at altitude
- . Exercise may be beneficial although some clinicians counsel the avoidance of rowing, golf, tennis, skiing, squash, or any other vigorous and repetitive resistance sports (there is no published evidence to this effect)
- . Some experts recommend the use of compression garments during exercise
- . Maintenance of ideal body weight should be encouraged
- . Obesity is a contributing factor for lymphoedema and may limit the effectiveness of compression therapies
- . Skin infection should be promptly treated with antibiotics and, if recurrent, prophylactic antibiotics should be considered
- . Provision of a home supply of antibiotics could be supplied to be taken at the first sign of infection.

General comments:

This short guideline was based upon a systematic review of literature from Medline (1966-2000)

and CancerLit databases (1985-2000). Although the review was first intended to include only RCTs, the paucity of such studies led to a wider inclusion of review articles and book chapters.

A first draft of this guideline was developed by a task force which had been sponsored by the British Columbia Cancer Agency. The task force comprised physical therapists, breast surgeons, radiation & medical oncologists and breast cancer patients with lymphoedema. Updating and revisions were undertaken by a writing group and approved by the steering committee. There is no description of paper selection, screening or data extraction.

Recommendations:

- (1) Practitioners may want to encourage long-term and consistent use of compression garments by women with lymphoedema.
- (2) One randomized trial has demonstrated a trend in favour of pneumatic compression pumps compared with no treatment. Further randomized trials are required to determine whether pneumatic compression provides additional benefit over compression garments alone.
- (3) Complex physical therapy, also called complex decongestive physiotherapy, requires further evaluation in randomized trials. In one randomized trial no difference in outcomes was detected between compression garments plus manual lymph drainage and compression garments alone.
- (4) Clinical experience supports encouraging patients to consider some practical advice regarding skin care, exercise and body weight.

Johansson *et al.* (2005)

Design: Randomised crossover trial (other), evidence level: 2-
Country: Sweden

Inclusion criteria:

Unilateral arm lymphoedema secondary to breast cancer
Women ≤ 70 years
Limb volume 10-40% greater than the unaffected arm
Oedema must have occurred at least 3 months after surgery and have been present for at least 6 months.

Exclusion criteria:

Women with recurrence of breast cancer
Intercurrent disease in the affected limb
Any condition that would make it difficult to participate e.g. dementia, language limitations.

Population:

Number of patients = 31, age range 40 to 68 years, mean age = 55, median age = 54 years

Interventions:

Patients received a standard exercise program: using weights (0.5-1 kg) - shoulder flexion, abduction and horizontal adduction together with elbow extension and flexion.

2 weeks before the exercise program, patients wore compression garments either night and day or during the night, according to usual practice over the previous 3 months.

The exercise program extended over 5 days and included 2 training sessions with rest and measurements between sessions. Participants wore a compression garment (23-32 mmHG) in one session and not the other (with randomisation to determine the order in which this would occur).

Outcomes:

To determine the effect of exercise on the degree of lymphoedema.

Lymphoedema was measured by multiple frequency bioelectrical impedance (MFBIA) and water displacement (determined with reference to the contralateral, unaffected arm with corrections for asymmetry). MFBIA was used for only 10 patients.

Patient reported (subjective) sensations in the affected arm e.g. heaviness, tightness. They also completed a questionnaire reporting on the level of physical activity undertaken in the previous year.

Perceived exertion after physical exercise, measured on a Borg scale (from 6-20).

Follow up:

Baseline assessment of outcomes (other than the Borg scale) preceded the first exercise set after which the perceived exertion was measured. The set of exercises were repeated twice more with 2 minutes break between each session. After the third session, all outcomes (except the questionnaire) were repeated immediately and finally after 24 hours. The entire program was repeated after a days rest and outcomes (except for the questionnaire) were repeated in the same sequence.

Follow-up did not extend beyond 24 hours after completion.

Results:

Data analysis showed that the order in which the compression garment was worn during exercise was of no significance and hence the results were presented as only pre- and post-exercise outcomes.

Mean volume difference between affected vs unaffected arms was significant (2726 ± 404 ml vs 2331 ± 352 ml $P < 0.001$) at the start of the study, before exercise.

After exercise a significant increase in volume was found regardless of compression sleeve use ($P < 0.001$) but by 24 hours the volume had reduced and was no longer significant when compared to that before exercise.

The lymphoedema absolute volume (with reference to the unaffected arm) also increased immediately after exercise, but only when the compression sleeve was being worn, and fell after 24 hours to a level not significantly different from that before exercise. When expressed as a relative percentage, the affected limb volume decreased significantly after 24 hours for those participants not wearing a sleeve ($P < 0.05$).

Exercise caused a slight, non-significant increase in MFBIA for those participants wearing a sleeve, either after exercise or 24 hours later.

Subjective sensations: Patients reported heaviness (42%) and tightness (52%) in the affected arm either after exercise or 24 hours later.

Exertion: Patients rated the exercise program as 'very light' and judged exertion to have been non-significantly greater when the exercise was performed whilst wearing the sleeve.

General comments:

This paper reported a small crossover trial examining the effects of a structured exercise program on limb volume in arms affected by lymphoedema secondary to breast cancer therapy. The only element of randomisation, for which no methodology was given, was in which order the wearing of a compression sleeve would occur i.e. in the first or second exercise program.

The data show that wearing the compression garment actually contributed to the sometimes significant, albeit transient, increase in lymphoedema. None of the exercise effects were

assessed beyond 24 hours.

The results did not allow a firm recommendation to be made regarding the contribution of compression sleeves to the effects of exercise on lymphoedema. The authors could say that exercise was beneficial to the lymphoedema patient's overall health and that this particular exercise regime had no apparent adverse effects on the oedema.

The lack of exertion expressed by the participants led the authors to conjecture that the level of exercise intensity might be raised without undue harm but that this had not been assessed formally. They also point out that these participants had only relatively mild lymphoedema and therefore the results of this small trial might not be applicable to patients with more severe limb swelling.

Updated evidence (6.1)

Evidence statement

Three papers were identified to update the evidence on the management of lymphoedema in women with breast cancer. One systematic review (Rinehart-Ayres *et al.*, 2007) of studies involving the use of compression pumps found only one paper of value (Dini *et al.*, 1998) which has been previously appraised for this topic. The reviewers concluded that the use of an intermittent compression pump did not provide more benefit than education about arm care.

A phase II study (Kim *et al.*, 2007) described a standard program of CDT which included intensive treatment with manual lymph drainage (MLD) compression bandaging, remedial exercise and skin care followed by a home maintenance program. The authors were examining the quality of life (QOL) for women on this study and found significant improvements across time in elements of physical and mental abilities and functioning together with significant reductions in limb volume. Although hoping to show a positive association between lymphoedema response and QOL, this study was non-comparative and the patients were not randomised in their groups hence the conclusions drawn about a relationship between variables were purely speculative. Similarly, a retrospective case series (Koul *et al.*, 2007) found that therapy which included components of CDT was associated with significant reduction in arm volume which was evident one year after beginning treatment.

References

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Koul R., Dufan T., Russell C., Guenther W., Nugent Z., Sun XY and Cooke AL (2007) Efficacy of complete decongestive therapy and manual lymphatic drainage on treatment-related lymphedema in breast cancer. *International Journal of Radiation Oncology Biology Physics* **67**: 841-846

Rinehart-Ayres ME., Fish K., Lapp K., Nagle C and Rucker B (2007) Systematic review of the use of compression pumps for upper extremity lymphedema following treatment for breast cancer. *Rehabilitation Oncology* **25**: 25-

Evidence tables

Question: Lymphoedema in breast cancer patients who have completed treatment and have no active disease

Created by: Karen Francis on

Rinehart-Ayres <i>et al.</i> (2007)
Design: Systematic review (therapy) abstract only. Evidence level: 4 Country: United States of America
Inclusion criteria: Included studies: Randomised controlled trials Included patients: Upper extremity lymphoedema (after surgery or radiation therapy for breast cancer) Had received therapy provided by a physical therapist in a clinic Therapy had included the use of a compression pump Pre- and post-treatment measurements had been made of the lymphoedema
Exclusion criteria: None stated
Population: Number of patients = Not stated
Interventions: Compression pumps
Outcomes: To determine evidence to support the use of compression pumps in the treatment of upper extremity lymphoedema (after surgery or radiation therapy for breast cancer) and to identify a specific treatment regime that should be used.
Follow up: -
Results: See General Comments.
General comments: This review examined data from 8 RCTs on the use of a compression pump in the treatment of lymphoedema. The reviewers determined that the use of an intermittent compression pump did not provide more benefit than education about arm care. This evidence came from an old study (Dini <i>et al.</i> , 1998) since other papers reviewed were, in their opinion, too methodologically flawed for inclusion. The paper in question was included in the original evidence review and hence this abstract offers no new information.

Kim <i>et al.</i> (2007)
Design: Phase II study (therapy). Evidence level: 3 Country: Korea
Inclusion criteria: Women at least 19 years old Unilateral upper limb lymphoedema No known neurological disorder that would affect completion of study Ability to complete questionnaire No history of treatment for any type of cancer No known untreated or unstable medical conditions No lower limb oedema Completion of adjuvant chemotherapy, radiation and surgery for breast cancer at least 3 months and not more than 5 years previously Written informed consent

<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 68. Age range: 44.3 to 57.7 years. Median age = 51 years</p>
<p>Interventions: Daily treatment from a physical therapist which included a decongestive phase (2-4 weeks depending on condition and patient's economic status) followed by a maintenance phase of self-care.</p> <p>Decongestive phase: manual lymph drainage (MLD) compression bandaging, remedial exercise and skin care. Each session lasted for up to 60 minutes and also included instructing the patients in self care activities (self administered MLD, exercise, bandaging and skin care) which were to be undertaken during the maintenance phase.</p> <p>Maintenance phase: Wearing compression bandages or hosiery at all times, daily session of MLD, skin care and exercise.</p>
<p>Outcomes: Reduction of lymphoedema: comparison of measurements of the affected arm made at baseline, 1 month and six months after therapy by a trained physical therapist, using a tape measure, and including girth and length. Volume calculations were calculated and the changes from baseline through follow-up which were expressed as percentage excess volume (PCEV) differences.</p> <p>Quality of life (QOL): patients completed baseline and follow-up (1 month and 6 months after decongestive therapy) SF-36 questionnaires. This has 8 sub-scales: physical functioning, role-physical, role-emotional, mental health, bodily pain, general health, vitality and social functioning.</p>
<p>Follow up: Five patients failed to visit the clinic for follow-up, one patient died and nine patients refused to complete the questionnaire and volume measurements or were too ill to comply.</p> <p>Follow-up consisted of visits scheduled at 1 and 6 months.</p>
<p>Results: QOL – functional status: Physical functioning: P = 0.004 (at 6 months vs baseline) Social functioning: P = 0.098 (NSD) Role-physical: P = 0.001 (at 6 months vs baseline) Role-emotional: P = 0.184 (NSD)</p> <p>QOL – wellbeing: Mental health: P = 0.004 (at 1 month vs baseline) Vitality: P = 0.250 (NSD) Bodily pain: P = 0.782 (NSD) General health: P = 0.02 (at 6 months vs baseline)</p> <p>PCEV differences between affected and normal arms: Baseline = 49.28 ± 21.98% 1 month = 28.66 ± 11.29% 6 months = 41.64 ± 17.31% (P < 0.05 comparing baseline with either follow-up measurement and also 6 months with 1 month follow-up measurements).</p>
<p>General comments: This paper describes a modest prospective study of complex decongestive therapy with a maintenance program for which patients were enrolled between March 2003 and October 2005 at three outpatient clinics in Korea.</p>

Lymphoedema measurements made 1 month after decongestive therapy showed a decrease in the percentage volume difference between affected and normal arms but at 6 months, whilst still statistically significant, the volume difference between arms was much reduced.

The QOL assessments showed significant improvements across time in elements of physical and mental abilities and functioning. The authors made a comparison between limb volume reduction and QOL (data not shown) and found that reduction in lymphoedema volume correlated to increases in QOL. They theorised that the improvement may have been as a result of the CDT program although this is highly speculative since other factors are likely to have contributed and, indeed, some of the SF-36 sub-scales were not significantly changed over time.

Koul *et al.* (2007)

Design: Retrospective case series (therapy). Evidence level: 3
Country: Canada (federal state, Commonwealth Realm)

Inclusion criteria:
 Women who had lymphoedema secondary to breast cancer
 Patients who had ≥ 1 year follow-up after lymphoedema therapy

Exclusion criteria:
 None stated

Population:
 Number of patients = 138. Age range: 29 to 82 years. Mean age = 54.3 years.

Interventions:
 Intensive phase (CDT): Manual lymphatic drainage (MLD), compression therapy, remedial exercises for the arm & shoulder and deep breathing to promote venous and lymphatic flow.

Home program: including training to do self-lymphatic drainage, education on skin care and remedial exercise. No patients received pneumatic compression therapy.

Maintenance phase: After the home therapy phase was completed patients were given a custom made compression garment and moved into the permanent home care phase. The compression garment was to be worn daily whilst awake and remove at bedtime. The patients were also encouraged to perform simple lymph drainage every day.

Outcomes:
 Reduction in lymphoedema measured as percentage difference between affected and unaffected arms.

Follow up:
 Baseline assessments included physical examination and measurements of the circumference of both arms together with subjective symptoms of tightness, numbness, stiffness and heaviness. The lymphoedema severity was graded according to the percentage difference in volume between the affected and unaffected limbs. Follow-up measurements were made weekly during the intensive phase of therapy.

Patients were interviewed by telephone 3 months after treatment. Follow-up measurements were done at 6 months and 1 year.

Results:
 76 women followed all four CDT components. 44 women received MLD alone and 18 patients with only mild lymphoedema, received instructions and counselling for the home program.

Arm measurements for all patients:

Mean pre-treatment volume of affected arm baseline = 2929 ml (range: 1474-5879)

Mean pre-treatment volume of affected arm after 1 year = 2741 ml (P < 0.0001)

Mean pre-treatment volume of unaffected arm 2531 (range: 1320-4299)

Mean pre-treatment volume of unaffected arm 2509 ml (NSD)

Mean difference between arms at baseline = 398 ml ± SD (469 ml)

Mean difference between arms at baseline = 232 ml

Arm measurements for patients receiving entire CDT program:

Mean pre-treatment volume of affected arm baseline = 3074 ml

Mean pre-treatment volume of affected arm after 1 year = 2852 ml (55.7% reduction)

Arm measurements for patients receiving MLD only:

Mean pre-treatment volume of affected arm baseline = 2778 ml

Mean pre-treatment volume of affected arm after 1 year = 2613 ml (41.2% reduction)

Arm measurements for patients receiving home program only:

Mean pre-treatment volume of affected arm baseline = 2685 ml

Mean pre-treatment volume of affected arm after 1 year = 2587 ml (24% reduction)

(P < 0.0001 between groups)

General comments:

This paper presents the data from a large retrospective review of data from case files of women who were treated with MLD and/or CDT for upper limb lymphoedema. The therapy was given by one of only two therapists at a single outpatient clinic between ~1999 and ~2001. 29/138 women had stage III/IV breast cancer.

CDT was offered to patients with moderate to severe lymphoedema and these women had the best response, measured by limb volume reduction. Those patients who were only enrolled in the home program had only mild lymphoedema and showed a less dramatic response to therapy.

The authors concluded that a program which offered some or all of the components of CDT was associated with significant reduction in arm volume which was evident one year after beginning the therapy. Unfortunately, as the authors point out, without a comparative control group it would not be possible to state with certainty that such reductions might not occur without intervention in these patients. In addition the lack of randomisation into the three treatment sub-groups means that it would not be possible to form any conclusions about their comparative efficacy hence the evidential value of these findings is only weak.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

6.2 Uncontrolled local disease

Short summary

The standard of publications on the topic of uncontrolled local disease was very poor comprising seven low patient number case series (Bower *et al.*, 1992; Kuge *et al.*, 1996; Lund-Nielsen *et al.*, 2005; Kumar *et al.*, 1987; Kolodziejcki *et al.*, 2005, Faneyte *et al.*, 1997 and Pameijer *et al.*, 2005), the majority of which were retrospective. Whilst the studies concerned women with breast cancer, some with wounds clearly classified as fungating, others with local recurrence in the chest wall, the evidence was considered inadequate and a position paper was commissioned.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with operable fungating lesions	<ul style="list-style-type: none"> • Simple resection + RT or systemic therapy • Simple resection + RT + systemic therapy • Major resection and repair of chest wall with flaps 	Simple resection ± RT	<ul style="list-style-type: none"> • Improved local control and overall survival • QOL • Morbidity – social isolation • Symptom control – pain, bleeding, odour • Self esteem
Patients with inoperable fungating lesions	<ul style="list-style-type: none"> • RT + systemic treatment • Topical agents – miltefosine • Dressings (charcoal, metronidazole, intrasite, maggots) 	Systemic treatment ± RT	<ul style="list-style-type: none"> • Physical and social functioning

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

The evidence base for this question is poor. Seven studies were identified and were all low patient number case series, four of which were retrospective. All the studies concerned women with breast cancer, some with wounds clearly classified as fungating, others with local recurrence in the chest wall. Treatments were occasionally given with curative intent when patients had no clinical evidence of metastatic disease. The small patient base is therefore broadly comparable with the population of the question.

Metronidazole for the elimination of odour from fungating lesions:

Two papers addressed this issue in a research setting. Bower *et al.* (1992) attempted to run a prospective trial on the use of metronidazole gel against a placebo gel but, unfortunately, the patient number was far too low (n = 9) to make any claims of more than anecdotal value. Patients and therapists reported improvement in odour control for both intervention and placebo groups over a few days. The increased washing and dressing of wounds in the study protocol may itself have contributed towards this result and hence masked any benefit of the intervention.

Kuge *et al.* (1996) reported another very low patient number (n = 5) prospective case series to test metronidazole gel. At that time in Japan this gel was not commercially available and so the

authors designed their own version according to the manufacturer's ingredients. By means of wound swabs they quantified the bacterial load before and after topical application of their gel. They determined that the malodour was improved after a few days due to the elimination of anaerobic bacteria e.g. *Peptostreptococcus*, *Bacteroides* spp.

Evaluation of a wound care regime to control odour and seepage from malignant wounds:

One paper (Lund-Nielsen *et al.*, 2005) tested a fungating wound care regime on a small group (n = 12) of patients with advanced breast cancer. Three patients were not receiving other therapy but were being treated with palliative intent whereas the remaining patients were receiving systemic therapy for their disease. The regime under scrutiny included wound cleaning, application of a wound care product of the patient's choice, use of a protective covering, such as film or hydrogel, and then wound dressing. Details of the various products are elaborated and reviewed but were not tested against one another. The outcomes reported were wound size, patient comfort and control of odour, bleeding and seepage. The authors claim that 75% of the patients reported a considerable benefit from the regime as a whole. However, patients with end-stage disease did not report such a benefit whilst those with a positive outcome were concurrently receiving active treatment, meaning that it is not possible to say with certainty that the observed benefit was due to the intervention rather than to the effects of systemic therapy.

Chemotherapy–surgery–chemotherapy for the treatment of locally advanced fungating breast cancer:

One paper (Kumar *et al.*, 1987) reported a study of 30 patients with locally advanced and inoperable fungating disease who were treated with a set protocol of chemotherapy before and after surgery. Initial therapy was combined cyclophosphamide, methotrexate, prednisone and 5'-fluorouracil over a 14 day cycle (2 cycles) followed by surgery (modified or simple mastectomy) and further cycles of chemotherapy (6 cycles). It is clear that the initial chemotherapy provided the opportunity for the lesion to be resected in many patients (n = 25/30). After one year a third of all patients were without disease recurrence but many others were unaccounted for. No statistics were presented for survival and details of patient characteristics, tumour evaluation and adverse events are scant.

Full thickness chest wall resection (FTCWR) of recurrent locally advanced breast cancer:

Three studies (Kolodziejcki *et al.*, 2005, Faneyte *et al.*, 1997 and Pameijer *et al.*, 2005) described outcomes and methodologies for chest wall resection with reconstruction in a total of 79 patients. Kolodziejcki *et al.* (2005) presented a small (n = 13) retrospective case series in which patients received FTCWR for breast cancer recurrence which included at least one rib and/or the sternum and involved all layers of the chest wall. Reconstruction varied according to patient but included flaps from neighbouring tissues, different muscle groups, contralateral breast tissue or omentum supported in some cases with mesh. Authors reported the survival rate at 5 years as 62% but it must be noted that patients with known distant metastases were excluded from this study and hence the patients as a group might be expected to have a better prognosis than otherwise.

Similarly Faneyte *et al.* (1997) excluded patients with distant metastases and performed FTCWR and reconstruction which included the same methodologies as Kolodziejcki *et al.* (2005) with the exception of the use of implants and in 7 cases, primary closure (which might suggest smaller post-operative wounds?). The authors selected only case files of patients that had a 'long disease-free interval between primary therapy and recurrence' and were not of 'advanced age', neither criterion were elaborated. Presumably such patients were expected to have a better prognosis - the median overall survival for all patients was 4.8 years. The survival rate at 5 years was 45%.

Pameijer *et al.* (2005) examined case files from 22 patients in a retrospective study of FTCWR for post-mastectomy local recurrence of full thickness chest wall, ribs and/or sternum. The inclusion

and exclusion criteria were not given but authors did state that patients with distant metastases were treated with palliative intent and otherwise with curative intent. The survival rate at 5 years was 71% with a disease-free rate of 67%. Those patients who had wound complications had a much shorter mean overall survival of 3.7 years compared with those who had no surgical complications and a mean overall survival of 6.2 years. The authors also included a self termed 'meta-analysis' but which was a summary of data from other similar studies. Patient characteristics and intervention methods were not presented and hence combining these data in a non-systematic way could well be irrelevant given that the actuarial survival rates varied across studies from 18% to 71%. For this reason the outcomes were not reported here.

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Lund-Nielsen B., Muller K and Adamsen L (2005) Qualitative and quantitative evaluation of a new regimen for malignant wounds in women with advanced breast cancer. 6412725. *J Wound Care* **14**: 69-73.

Pameijer CR., Smith D., McCahill LE., Bimston DN., Wagman LD and Ellenhorn JD (2005) Full-thickness chest wall resection for recurrent breast carcinoma: an institutional review and meta-analysis 371. *Am Surg* **71**: 711-715.

Evidence tables

Question: Management of patients with operable or non-operable fungating lesions
Created by: Karen Francis on 03/04/2007

Bower <i>et al.</i> (1992)
Design: Prospective case series (therapy), evidence level: 3 Country: United Kingdom
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 9, age range 51 to 85 years, mean age = 68 years

Interventions:

Intervention: 0.8% metronidazole gel at 1g per cm² lesion area

Comparator: Placebo gel

Both gels were applied daily for 6 days. After this time treatment was open for all patients at a variety of treatment doses according to individual requirements. This was continued for 5 days.

Outcomes:

To test the efficacy of metronidazole gel in successfully reducing or eliminating the odour of fungating wounds as assessed by the patient and one investigator after 6 days of treatment.

The visual analogue scale (0-10) was used for grading response to odour by the patient and by the investigator.

Follow up:

Initial grading of odour was (for all patients presumably) a minimum of 6/10 on the visual analogue scale.

2/11 patients were withdrawn before the end of the trial period.

Results:

Odour was graded throughout the first 6 days by patients and on day 6 by staff.

Intervention (n = 5):

Mean grading by patients and staff ≥ 6

Placebo (n = 4):

Mean grading by patients = 5

Mean grading by staff = 4.3

There was no significant difference between intervention and placebo at this stage.

Open assessment results after a further 5 days:

Patients originally randomised to the intervention (n = 5):

Mean grading by patients = 2.3

Mean grading by staff = 1.5

Patients originally randomised to the placebo (n = 4):

Mean grading by patients = 1.2

Mean grading by staff = 1.1

Authors reported the improvement from day 0 to day 11 as $P < 0.001$ for both patient and staff assessments for all patients.

General comments:

This is a poor quality study and the patient number is far too low for any statistical significance. There are no details of randomisation, allocation, blinding etc. Therefore, this study has been graded as a prospective case series rather than as a RCT.

11 patients were enrolled but 2 were withdrawn due to their requirement for systemic therapy which was not otherwise given to patients during this trial or for four weeks prior to its commencement.

9/11 patients had breast cancer.

Unfortunately the very low patient number renders the results of little significance and the positive results for the placebo group may well have arisen as a result of daily cleansing and dressing as part of the trial protocol. Higher patient numbers may have revealed a true significance for this intervention.

Kolodziejski *et al.* (2005)

Design: Observational study (prognosis), evidence level: 3

Country: Poland

Inclusion criteria:

Single focus of local recurrence

Ability to undergo FTCWR with 3 cm clear margins

Exclusion criteria:

Distant metastases

Serious respiratory disorders

Population:

Number of patients = 13, age range 29 to 67 years, median age = 58 years

Interventions:

Full thickness chest wall resection (FTCWR) for local post-mastectomy breast cancer recurrence, defined as recurrent tumour destroying or surrounding at least one rib and/or the sternum. Only patients with all layers of the chest wall invaded by recurrence were offered this treatment.

Methodology varied according to the patient but all surgery was undertaken by one reviewer. All chest wall defects were repaired using soft tissue and 3/13 patients had a mesh support. Skeletal defects were not repaired - this was attempted but abandoned due to local reaction.

Outcomes:

Kaplan-Meier analysis was used to estimate median overall survival (OS)

Follow up:

Mean follow-up was 66 months, median follow-up was 54 months (range: 9-144) which was long enough to report on the median OS at 5 years.

Results:

Mean diameter of chest wall defect = 12 cm

3 patients died at 15 months, 40 months and 54 months after disease dissemination. One patient died from unknown cause at 124 months. 2 patients are alive with distant metastases after 136 and 132 months. 6 patients are alive with no evidence of disease after a mean follow-up of 57 months.

No patient suffered recurrence at the site of surgery. The clearance margin was 3cm.

Reconstruction type:

Contralateral breast (n = 5) (NED = 2)

Omentum-mesh-omentum (n = 1) (alive but with metastases)

Epigastric & axillar cut-subcutaneous flap (n = 2) (NED = 1)

Mesh + serratus & latissimus muscle (n = 1)

Neighbouring tissues (n=2) (NED =1; alive but with metastases = 1)

Mesh + pectoral muscles (n = 1) (NED)

Major pectoral muscle (n = 1) (NED)

(NB NED = no evidence of disease)

Median OS rate at 5yrs = 62%

General comments:
 This paper observes the outcomes of 13 women who had received FTCWR for breast cancer recurrence at a single treatment centre between 1983 and 2001.

Median age of patient group had been 44 years at the time of mastectomy, which was followed by chemotherapy (n = 7), RT (n = 6), hormone therapy (n = 1) or no further treatment (n = 3).

This group elected not to perform this chest wall surgery on patients with distant metastases.

The long term survival rates may reflect the carefully selected population, which had no evidence of metastatic disease and were chosen on the basis of favourable pre-operative assessment.

Kuge <i>et al.</i> (1996)
Design: Prospective case series (therapy), evidence level: 3 Country: Japan
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 5, age range 47 to 71 years, median age = 59 years
Interventions: 0.8% metronidazole gel of unknown dosage was spread onto dressings and applied once or twice daily. Treatment was continued for between 6 and 131 days (median 37 days) but was assessed at the time of efficacy.
Outcomes: Odour was assessed by the patient, doctor and nurse. No scale was used but the date when the odour disappeared was recorded. Adverse events were also recorded by the doctor.
Follow up: Swabs were taken before treatment and assessed for aerobic and anaerobic bacterial load and species identification (ANA II or API rapid systems). Post therapy swabs showed the elimination of anaerobes but not aerobes or 'facultatives' (facultative anaerobes). Treatment was continued until the day of death (n = 3), mastectomy (n = 1) or beyond the date of publication (n = 1).
Results: Malodour disappeared from 4 patients (advanced breast cancer) within a median time of 4 days (range: 2-5) and in the 5th patient (recurrent breast cancer) by day 4. Opinions were unanimous between patient, doctor and nurse. There were no adverse events.
General comments: This study is a small prospective case series of patients admitted with fungating breast cancer at a single treatment centre between March 1995 and July 1995.

The low patient number and lack of quantitative measurements render this paper of little evidential value. Anecdotally, the gel appears to have been very effective in removing malodour from these patients without adverse effects.

Faneyte *et al.* (1997)

Design: Retrospective case series (prognosis), evidence level: 3
Country: Netherlands, the

Inclusion criteria:
Long disease-free interval after primary treatment
No distant metastases
Young age (not defined)
Pain and ulceration

Exclusion criteria:
Carcinomatous lymphangitis
Multifocal recurrence
Insufficient pulmonary function
Distant metastases
Advanced age (not defined)
Disease-free interval < 5 years

Population:
Number of patients = 44, age range 31 to 79 years, median age = 57 years

Interventions:
Full thickness chest wall resection (FTCWR) for local post-mastectomy breast cancer recurrence.

Outcomes:
Median post-resection disease-free interval (PFI)
2yr and 5 yr disease-free rates
Survival (OS) analysed by Kaplan Meier method.

Follow up:
Median follow-up after FTCWR was 3.2 years. No patients were lost to follow-up.

At the time of publication, 21/44 patients were alive and 5 of these were free of tumour. Cause of death for 23 patients was associated with the primary cancer (n = 19), uncontrolled local disease (n = 1), metastatic disease (n = 18), myocardial infarction (n = 1), cerebrovascular accident (n = 1) and unknown causes (n = 1).

Results:
Clearance margins were 2cm or, if possible, up to 5cm.

Reconstruction type:
Contralateral breast (n = 3)
Myocutaneous latissimus dorsi flap (n = 2)
Stability using steel wire (n = 9)
Use of resorbable Vicryl mesh (n = 12)
Use of permanent Marlex mesh (n = 20)
Transposition of omentum (n = 1)
Primary closure (n = 7)
Other (n = 3)
Split skin grafts were used in 28 patients. 41 patients had implants.

Following surgery:
7 patients had wound infections

8 patients had pulmonary complications
5 patients need longer than usual (2 days) intubation
2 patients had necrosis of skin graft
1 patients had necrosis of the pedicle flap
10 patients required surgery for their complication. Risk of complication was unrelated to patient age.

12 patients received systemic therapy after surgery due either to incomplete resection or for metastatic disease. 8 patients received endocrine therapy, 2 RT and 2 received both.

Median OS of all 44 patients = 4.8 years
Survival rate at 5 years = 45%

30/44 patients had FTCWR with curative intent. Of these, 18 patients had tumour recurrence at the surgical site, 6 had a new local recurrence, 12 patients developed distant metastases and 5 patients had both local recurrence and distant metastases.

Median PFI for all 30 patients = 3.3 years.
Disease-free survival rate at 2 years = 60%
Disease-free survival rate at 5 years = 35%
Survival rate at 5 years = 58%

14/44 patients had FTCWR with palliative intent. 4 of these patients had doubtful histology on the resection margins.

Median OS = 2.3 years
Survival rate at 5 years = 21%

General comments:

This paper describes a retrospective review of case files of patients who had received chest wall resection for recurrent breast cancer at a single centre between 1979 and 1995.

Mean patient age at first diagnosis had been 47.5 years. Primary treatment was surgery (n = 43), RT (n = 28), chemotherapy (n = 6) or hormone therapy (n = 2).

This study was thoroughly researched but is still retrospective and therefore has limitations. The statistics and survival analyses are appropriate although outcomes are reported as point estimates.

Authors stated that patients undergoing FTCWR with curative intent had a significantly improved survival time (P = 0.008) and that younger (< 35 years) at first diagnosis had significantly shorter survival after FTCWR (P = 0.02). Associations between outcome and older age or the presence of distant metastases were not significant. They add that patients having a recurrence after initial treatment of less than 2 years may be contraindicated for this surgery as their disease-free interval was significantly shorter (P = 0.0001).

Kumar *et al.* (1987)

Design: Retrospective case series (prognosis), evidence level: 3
Country: India

Inclusion criteria:

Locally advanced fungating breast cancer
Unsuitability for surgery as primary therapy
Presence of distant metastases was acceptable.

<p>Exclusion criteria: Prior radiotherapy or chemotherapy.</p>
<p>Population: Number of patients = 30</p>
<p>Interventions: Patients received 2 cycles of combination chemotherapy before surgery: Cyclophosphamide at 150 mg on days 1-14 Methotrexate at 10 mg on days 1-5 Prednisone at 30 mg on days 1-14 Fluorouracil at 500 mg iv on days 1-5 14 days rest then cycle repeated.</p> <p>Following chemotherapy, patients were given simple or modified mastectomy followed by a further 6 cycles of the combined chemotherapy.</p>
<p>Outcomes: After initial chemotherapy, patients were evaluated for: Degree of mobility of the lesion mass Degree of mobility of nodes Reduction of ulceration of the mass Relief of odour, bleeding, well-being, dyspnoea & oedema</p> <p>Following surgery and further chemotherapy, the outcomes were tumour response: complete response (CR), partial response (PR), no response (NR) or progressive disease (PD) and adverse events.</p>
<p>Follow up: Baseline appraisal is described as a 'thorough clinical, haematological, radiological and biochemical evaluation' with no other details.</p> <p>Tumour biopsy was performed and samples examined histologically. Results were compared with post-operative specimens.</p> <p>Follow-up was at monthly intervals but the median term per patient is not stated. The results are reported for 1yr survival.</p>
<p>Results: Tumour response after pre-surgical chemotherapy: n (%) CR = 8 (26.67) PR (operable) = 10 (33.33) NR (still operable) = 7 (23.33) PD (inoperable) = 5 (16.67)</p> <p>25/30 patients went on to have either a simple mastectomy or mastectomy with axillary clearance.</p> <p>Following surgery and 6 cycles of post-surgical chemotherapy, after 1 year there were 10 patients with no evidence of disease (33.33%). 4 patients had disease recurrence. 2 patients died from leukopenia and 1 patient was lost to follow-up. It is not clear what happened to the remaining 13 patients.</p>
<p>General comments: This paper presents data from a (probably) retrospective study which occurred between 1983 and 1984 of patients in India that were treated for fungating breast cancer. No patient characteristics were reported.</p>

This simple, outdated study is of poor quality offering no statistics. Not all patients were accounted for.

Pameijer *et al.* (2005)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States

Inclusion criteria:

None stated

Exclusion criteria:

None stated

Population:

Number of patients = 22, age range 28 to 74 years, median age = 56 years

Interventions:

Full thickness chest wall resection (FTCWR) for local post-mastectomy breast cancer recurrence, defined as recurrent tumour including full thickness rib and/or the sternum.

Outcomes:

Median post-resection disease-free interval (PFI)

5 yr disease-free and overall survival rates

Follow up:

1 patient died from myocardial infarction.

No details of follow-up were presented.

Results:

All patients had FTCWR to grossly negative margins. 59% patients had pathologically negative margins.

Reconstruction type:

Myocutaneous flap (n = 19)

Marlex mesh (n = 9)

Gortex mesh (n = 11)

Following surgery:

7 patients had wound complications (their median survival was 3.7 years, compared to 6.2 years for those patients without complications)

After FTCWR patients received chemotherapy (n = 15), endocrine therapy (n = 9) or RT (n = 5)

Median PFI = 3.7 years

Survival rate at 5 years = 71%

Disease-free survival rate at 5 years = 67%

There were no significant prognostic factors for survival between previous treatment, nodal status or disease-free interval after primary therapy.

General comments:

This paper describes a retrospective review of case files of patients who had received chest wall resection for recurrent breast cancer at a single centre between 1970 and 2000.

The intent of the FTCWR was categorised as being either palliative or curative, based on the notes of the physician in the case file. Any patient with metastases was classed as receiving palliative therapy.

Primary therapy for breast cancer had included mastectomy (n = 18), RT (n = 8), chemotherapy (n = 10) or endocrine therapy (n = 4)

This paper offers little evidence despite including a 'meta analysis' which is a comparison and combination of 5 year survival rates from seven other studies. The methodology is not systematic; there is no comparison of patient characteristics across studies; no test of heterogeneity to determine whether such a study is statistically feasible - the 5 year actuarial survival rates varied from 18% to 71%. These data are not considered further here.

Lund-Nielsen *et al.* (2005)

Design: Hybrid Study (qualitative and quantitative study designs used) (therapy), evidence level: 3

Country: Denmark

Inclusion criteria:

None stated

Exclusion criteria:

None stated

Population:

Number of patients = 12, age range 57 to 85 years, mean age = 69 years

Interventions:

Wound care regime:

1. Rinse wound with tap water (sterile if bone exposed)
2. Wash unclean wounds with soap using foam washcloth then rinse under shower or with syringe
3. Note wound details incl. size, colour, seepage, smell, patient-reported pain, infection and bleeding
4. Apply chosen wound care product (patient choice)
5. Protect wound edges with barrier cream and/or film
6. Dress wound

Wound dressings:

- a) Hydrogel for dry necrotic wounds and use foam dressing
- b) Alginate dressing for seeping wounds and use foam dressing with adhesive border
- c) Charcoal dressing for malodorous wounds - on top of alginate or hydrogel if used or directly onto the wound if not then apply a foam dressing with adhesive border (unless patient is sensitive to adhesive). If adhesive dressing cannot be used then cover dressing with tube gauze or body netting.

Outcomes:

Wound recording:

Size and degree of healing were assessed before, during and at the end of the study. This was achieved by means of photographs and physical measuring. Malodour, seepage and bleeding extent were also recorded. The intervention was considered successful if the wound was reduced in size by more than 0.5 cm, if there was tissue granulation or presence of new epithelium and if malodour, seepage and bleeding were reduced or eliminated.

Dressings efficacy:

Functionality of the dressings was recorded by staff but included the patient perception in terms of comfort, functionality, number of changes, degree of absorption and containment of seepage and odour.

Patient perspectives were obtained by means of interviews before and after the treatment. Responses were sorted into themes by virtue of the use of certain verbal expressions. Interviews were undertaken either at home or in the hospital at the choice of the patient.

Dressings:
Functionality was assessed by staff.

Follow up:

-

Results:

Wound size:

9/12 patients showed a reduction in wound size, showed granulation or new epithelial tissue. 1/12 patient had a wound which healed completely. 3/12 patients had an increase in wound size with additional necrosis and infection (all three were not receiving active therapy).

Malodour:

7/12 patients had no malodour

2/12 had slight malodour

1/12 had the same malodour

2/12 had worse malodour

8/12 patients assessed their wounds as being more malodorous than was recorded by staff. After treatment 3/12 women detected malodour not recorded by staff, 3/12 women detected malodour which was detected by staff and 6/12 thought the malodour had a positive effect on malodour.

Bleeding:

11/12 patients registered no bleeding at the beginning or end of the regime but 1/12 patient experienced an increase in bleeding by the end. More (67%) women registered a perception of bleeding than was recorded by staff (8%).

Seepage/comfort:

Observers recorded a positive effect on 10/12 patients in whom seepage was either stopped or reduced considerably. 2/12 patients experienced a worsening of seepage. All participants experienced a reduction in dressing changes with an average reduction of 75%. Overall, all women felt that seepage was contained after treatment.

General comments:

This study investigates the efficacy of a wound care regime in terms of both qualitative and quantitative outcomes. Nevertheless, there are no statistical methods and hence the results are anecdotal.

Nine patients were receiving therapy for their disease but three patients had end-stage disease and were receiving palliative therapy only.

The authors conclude that 75% of patients received a considerable benefit from this regime but the patients with end stage disease did not record such an improvement. It would not be possible to state with certainty, therefore, that the positive results were due to the intervention rather than the anti-cancer therapy that the majority of patients were also receiving.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

6.3 Cancer- Related Fatigue

Short summary

Evidence on the management of cancer related fatigue (CRF) comprised two systematic reviews (Minton *et al.*, 2007 and Cramp & Daniel, 2008) one on drug therapies and one on exercise regimes, together with two RCTs (Headley *et al.*, 2004 and Bordeleau *et al.*, 2003) and a poor quality case series (Carson *et al.*, 2007).

Good evidence showed no significant effect of progestational steroids, including megestrol acetate, compared with placebo in the treatment of CRF.

Meta-analysis of data from 28 RCTs showed a highly significant effect of exercise compared with controls on fatigue reduction both in cancer patients as a whole and in a large sub-group with breast cancer. Since the review included all forms of exercise, a specific regime, intensity or duration could not be recommended.

There were no positive outcomes from a yoga program, seated exercise activity or weekly support group meetings with respect to improving levels of fatigue as assessed by standard measurement tools. No papers were identified to determine the effectiveness of cognitive behavioural therapy or psychotherapy in patients with advanced breast cancer.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Advanced breast cancer patients with a diagnosis of cancer-related fatigue in the absence of any remediable physical or psychological cause	<ul style="list-style-type: none"> • Low dose Corticosteroids (dexamethasone, prednisolone, prednisone) • Megestrol acetate • Education about fatigue, sleep, lifestyle, relaxation techniques. • Cognitive behavioural therapy (CBT) • Information about nutrition and hydration guidance • Complementary therapies • Use of a cancer-related fatigue tool 	Compared with nothing	<ul style="list-style-type: none"> • Reduced fatigue • Physical wellbeing • Emotional wellbeing • Ability to enjoy life in the moment • Ability to work • Intimacy with partner • Ability to take care of the family • Ability to enjoy relationships with family and friends • Improved quality of life • Reduced contact with health care practitioners • Economic costs

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

The evidence base for this question is very poor. Only three papers were identified that described studies which had recruited women with advanced or metastatic breast cancer. Two of these looked at interventions which were designed to help with general quality of life but also listed fatigue as one of the parameters under consideration.

One small RCT (Headley *et al.*, 2004) compared a seated exercise program with the normal activity undertaken by a control group. The participants had been recruited in a variety of ways but all were scheduled to receive outpatient chemotherapy for metastatic breast cancer. The principal outcome was fatigue and also quality of life using the FACIT-F questionnaire. Over the study period of twelve weeks it was found that the scores for physical and functioning parameters had declined but those for social functioning had not changed significantly. Although participants in both arms experienced increasing fatigue with therapy and/or disease progression the increase was significantly less marked in the intervention group ($P = 0.008$). However, the authors pointed out that as there were a significantly higher proportion of married women in the intervention arm there was a possibility of confounding because enhanced social support may have affected the outcomes.

Bordeleau *et al.* (2003) detailed a moderate sized RCT ($n = 235$) in which women with metastatic breast cancer were randomised to participate in a program of weekly support group meetings. These were led by a qualified psychotherapist and adhered to the principles of supportive-expressive theory which encouraged the women to express their emotions about how the cancer had affected their lives and those of their family and friends. Although this study was not specifically aimed at treating cancer-related fatigue, measures of fatigue were included as part of an overall appraisal of the scheme with relation to quality of life. The follow-up covered a period of a year post randomisation and did not highlight any significant advantage in any quality of life parameter for the intervention compared with the control (no support group). Unfortunately, the EORTC-QLQ-C30 assessment tool asks more questions on physical, rather than psychosocial, well being and may not have been sufficiently sensitive to have picked up changes in the outcomes of interest over the study period. The attrition rate of this trial was very high (~90%) due to the death of patients over the one year follow-up period, which means that the statistical power of the final analyses was very much lower than the study design had intended.

Carson *et al.* (2007) described a small ($n = 21$) prospective case series of women with metastatic breast cancer who participated in an eight week 'Yoga of Awareness' program that had been specifically designed to combat fatigue, pain and distress and heighten feelings of acceptance and relaxation. This was a very thoroughly conducted study where participants kept daily diaries, the data from which were analysed in numerous ways most of which involved complex statistical methodology which was not explained in the text (although readers were invited to contact the authors in order to gain understanding). It was found that yoga significantly improved some daily outcomes (invigoration ($P < 0.01$) and acceptance ($P < 0.02$) but not others (fatigue, pain, distress or relaxation) over the course of the program.

The time spent in yoga practice could be significantly correlated to same-day improvement in pain ($P \leq 0.01$), invigoration ($P < 0.01$) and acceptance ($P < 0.02$) but not fatigue, distress or relaxation. However, it was not possible to confidently assert the same-day benefits of yoga practice since cause and effect could not be separated (for example if a patient had a day where she was experiencing less pain she might have spent longer doing yoga or conversely the length of yoga practice might have caused the reduction in pain). For this reason, the authors also conducted a lagged day analysis and showed that the day after yoga practice, significant improvements were made in patient pain ($P = 0.03$), fatigue ($P = 0.05$) and invigoration ($P < 0.01$). Although the findings were not of great statistical significance, the widespread consensus

of the participants was that the program was very effective at improving social and emotional well being, due possibly because of the group support. It was hoped that the program would continue indefinitely for that purpose.

References

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Evidence tables

Question: What is the role of cancer related fatigue management in ABC?
Created by: Karen Francis on 30/08/2007

Bordeleau <i>et al.</i> (2003)
Design: Randomized controlled trial (therapy), evidence level: 1- Country: Canada (federal state, Commonwealth Realm)
Inclusion criteria: Histologically confirmed breast cancer Presence of metastatic disease beyond the breast and ipsilateral axilla before study entry Consent of responsible treating physician Written informed consent of the patient
Exclusion criteria: Presence of brain or CNS metastases Expected survival > 3 months Active psychosis Untreated major depression Severe personality disorder Inability to write and speak English Current participation in a long-term therapist-led support group Living > 1 hour travel away from study entry
Population: Number of patients = 235
Interventions: Participants in the intervention arm (n = 145) joined a weekly 90 minute therapist-led support group which adhered to the principles of supportive-expressive therapy. Each group contained between 6-10 women and two leaders. These groups ran continuously and new members were added individually over time. The therapy was 'intended to foster support among group members and to encourage the expression of emotions about cancer and the effects on their lives.

Relationships with family, friends and the health care team were discussed, the effect of the disease and its treatment were evaluated and life goals and priorities were re-evaluated.'

Women in the control arm (n = 70) did not participate in a support group.

Every 6 months all women received educational materials about breast cancer and its treatment, relaxation and nutrition.

Outcomes:

The main outcome reported in this paper was that of the health-related quality of life (HR-QOL) assessed using the EORTC QLQ-C30 tool. This questionnaire comprises thirty items within five sub-scales (physical, role, emotional, social and cognitive functioning) three multi-item symptom sub-scales (fatigue, pain and emesis), a two-item global QOL sub scale and six single item sub-scales (financial effect, dyspnoea, sleep disturbance, appetite, diarrhoea and constipation).

Follow up:

Participants completed a battery of psychosocial questionnaires at baseline and were also assessed by interview. At this time point information was obtained about medical status and treatment.

Following administration by a researcher at baseline, the EORTC QLQ-C30 was mailed out to patients after 4, 8 and 12 months.

Two women were excluded from the trial after randomisation due to ineligibility and the data from 20 women were excluded from the HR-QOL analysis because either baseline or 4 month questionnaire responses were not available.

25/215 women completed all questionnaires - attrition was due to death more commonly than for any other reason and proportionally did not differ between study arms.

Results:

There were no significant differences in patient characteristics between the two study arms at randomisation.

There were no significant differences in baseline HR-QOL scores arms or during the 12 months after randomisation for any scale or sub-scale. There was a significant deterioration in both arms across time for many of the items of the EORTC QLQ-C30 including global QOL (P = 0.03), physical functioning (P = 0.0002), role functioning (P = 0.01), cognitive functioning (P = 0.04), dyspnoea (P = 0.007), appetite loss (P = 0.04), and fatigue (P = 0.003).

General comments:

This paper describes a trial for which participants were recruited between June 1993 and December 1997 by several treatment centres in Canada. 235 women were randomised centrally into two arms, one of which received a group psychosocial intervention and the other which did not.

The primary outcome of interest in this study was overall survival which was previously reported in another paper as being not significantly different between arms.

The intervention, whilst not specifically intended to counter cancer related fatigue, was concerned to treat quality of life issues, one of which was fatigue.

A considerably detailed missing data analysis was performed in which numerous models were used to 'fill in' data due to the high attrition rate. However, the final analysis still failed to show any significant benefit of this form of psychosocial support to women with metastatic breast cancer.

The results might well indicate a genuine lack of influence for the intervention. However, the HR-QOL tool, whilst sensitive enough to detect the decline due to advancing disease, might not have been appropriate to test this type of therapy due to its emphasis on physical, rather than psychosocial QOL-related outcomes.

An examination of the published study of the primary outcomes (The effect of group psychosocial support on survival in metastatic breast cancer. Goodwin *et al.* (2001) *NEJM* **345** (24): 1719-1726) indicated that fatigue, scored with the POMS tool, also failed to show a significant difference between intervention and control arms ($P = 0.35$).

Headley *et al.* (2004)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: United States

Inclusion criteria:

Women > 18 years
 Diagnosed with stage IV breast cancer
 English literate
 Scheduled to receive outpatient chemotherapy
 ECOG performance scale ≤ 2
 Being able to sit in a straight-backed chair for 30 min
 Having access to a TV and video recorder

Exclusion criteria:

Women receiving high dose chemotherapy for bone-marrow or stem cell transplantation
 Women who had received RT in the previous 2 months
 Women receiving hormone treatment
 Serum haemoglobin ≤ 8 g per dl
 Resting pain level > 2 on a 0-10 pain scale
 Symptomatic bone metastases

Population:

Number of patients = 38, age range 37 to 73 years, mean age = 51 years

Interventions:

A seated exercise programme for 30 min three times a week with a minimum of a one day break between sessions. The exercise regime was shown on a video "Armchair Fitness: Gentle Exercise" and comprised a 5 min warm-up, 20 min of moderate intensity repetitive motion exercises and a 5 min cooling down period. Participants sat in a straight-back chair and performed stretching and repeated flexions and extensions of the limbs, head and torso.

Control:

Participants did not engage in seated exercise but could continue their usual physical activity.

Outcomes:

Study participants completed monthly calendar logs, noting the time, date, intensity (measured on a Rating of Perceived Exertion scale), type and length of exercise undertaken.

Data from the FACIT-F questionnaires provided information about fatigue and the physical, social, emotional and functional aspects of QOL.

Follow up:

Fatigue and quality of life (QOL) were assessed at baseline and at the beginning of each treatment (every 12 weeks) for four cycles using the FACIT-F scale. Clinical information was added regarding treatment type, cycle number, weight, height, performance status, location of metastatic disease, tumour response to treatment, current pain and current medication.

Six women did not complete this study due to disease progression, initiation of radiotherapy or a decrease in performance status. Twenty-four women completed all 4 questionnaires.

Results:

Over time the FACIT-F scores decreased for both arms in total and in the physical and functioning sub-scales but not for the social functioning sub-scale. The emotional sub-scale increased across time but returned to baseline values by the study end.

Total mean FACIT-F scores:

At baseline:

Physical well-being = 23.84 ± 4.82

Social well-being = 20.88 ± 5.07

Emotional well-being = 15.39 ± 5.27

Functional well-being = 20.50 ± 5.12

Fatigue = 40.00 ± 10.95

Total score = 120.61 ± 22.87

Total mean FACIT-F scores:

At 4 cycles:

Physical well-being = 16.92 ± 8.45

Social well-being = 20.77 ± 4.80

Emotional well-being = 17.90 ± 4.45

Functional well-being = 19.33 ± 6.62

Fatigue = 35.93 ± 11.45

Total score = 114.83 ± 26.89

These results indicated to the authors that all QOL parameters were declining and that this rate was accelerating, by day 60 (approximately halfway through the study) regardless of group.

When the two arms were compared according to the non-standard analytical methodology, the authors found that although both groups were declining in QOL, the intervention group's decline was slower.

For the fatigue sub-scale a difference was found in the decline of scores over time with the intervention experiencing a slower decline ($P = 0.0078$). This was also true of physical well-being ($P = 0.0252$) but of no other sub-scales.

General comments:

This is a small RCT using non-standard but valid means of allocation and randomisation. The patient number was low and the analysis for the outcomes between arms was not shown in detail. The treatment effect was calculated by measuring the differences between two slopes constructed by plotting successive scores over time.

There were significant differences in education level and marriage status between the two arms at baseline. However, there were no significant differences in other patient characteristics including weight, tumour response or age. It was noted that more (8 vs 4) women randomised into the control group were regularly exercising at the time of study enrolment.

Participants were recruited to this study by non-probability consecutive sampling. Non-probability sampling techniques cannot be used to infer from the sample to the general population. Any generalizations obtained from a non-probability sample must be filtered through knowledge of the topic being studied. Performing non-probability sampling is considerably less expensive than doing probability sampling, but the results are of limited value.

The authors pointed out that since the intervention group comprised more married women,

spousal support may have been a confounding factor to significant outcomes.

Carson *et al.* (2007)

Design: Prospective case series (therapy), evidence level: 3

Country: United States

Inclusion criteria:

Women with metastatic breast cancer
Informed consent

Exclusion criteria:

> 6 months life expectancy
Change in anti-depressant use in past 6 months
Treatment for serious psychiatric disorders
Current intensive yoga therapy
Living more than 1 hour drive away from therapy centre
Non-English speaking

Population:

Number of patients = 21, mean age = 59 years

Interventions:

Eight week 'Yoga of Awareness' Program, designed for metastatic breast cancer patients. The therapy included gentle yoga postures, regulated breathing, guided meditations, didactic presentations and group discussions. The study was conducted by a qualified yoga instructor.

Patients kept prospective daily diaries, recording the outcomes on a 100 mm visual analogue scale. Data were analysed by means of a 'multi-level random effects model' claimed by the authors to identify within-person and between-person variation.

At the end of the study participants were invited to join a focus group to discuss their experiences.

Outcomes:

Measures of pain, fatigue, distress, invigoration, acceptance and relaxation were recorded at baseline, two weeks before therapy commenced, and each day during the last two weeks of the study.

Follow up:

Attrition was 28%. Before the start of the study 3 women withdrew (for reasons not related to health) and shortly after the start of the therapy 4 women left (only 1 with a health related cause). One more woman failed to complete the questionnaires (due to dementia). Therefore 13/21 women provided assessable data.

Results:

Treatment effects on patients' daily outcomes over time (from pre- to post- recording periods): There were significant improvements in daily invigoration ($P < 0.01$) and acceptance ($P < 0.02$) but not pain ($P = 0.10$), fatigue ($P = 0.16$), distress ($P = 0.44$) or relaxation ($P = 0.09$).

Length of yoga practice and same day outcomes:

In 71% of diaries, patients reported spending an average of 20 minutes per day in formally practicing yoga. An analysis was made of time spent in practice and whether or not this was predictive of variability in outcomes within that day. There were significant improvements in pain ($P < 0.01$), invigoration ($P < 0.01$) and acceptance ($P < 0.02$) but not in fatigue ($P = 0.07$), distress ($P = 0.55$) or relaxation ($P = 0.07$).

Length of yoga practice and lagged (next) day outcomes:

This analysis was done because the same day analysis could not show cause and effect between practice and, for example, pain improvement. In other words, pain reduction could have influenced the length of yoga practice or vice versa. Lagged day outcomes showed a significance between time spent in practice and improvements in next day pain ($P = 0.03$), fatigue ($P = 0.05$), invigoration ($P < 0.01$), acceptance ($P = 0.02$) and relaxation ($P = 0.03$) but not distress ($P = 0.97$).

[4] Focus group feedback:

There was widespread consensus that the number and length of yoga sessions, techniques imparted and overall content of the program were appropriate and very useful. Apparently, there were also remarks on the value of doing the training with other MBC sufferers, as opposed to a more heterogeneous group.

Several women voiced their opinion that the only improvement that could be made was to extend the length of the yoga training to allow ongoing monthly classes - both to gain advantage from the therapy itself and for the purpose of meeting women in a similar situation as themselves.

General comments:

General comments:

This paper presents a small trial of a yoga program, prepared especially for women with metastatic breast cancer.

Participants were found to have a wide range of baseline characteristics, for example previous treatment, general health, marital status, education, ethnicity etc.

Data analysis was by means of a statistical software package (SAS Proc Mixed, SAS Institute) for which little information was given on the interpretation of results. The results, therefore, are not reproduced here (although the authors invited enquiries if an explanation of the multilevel equations was required) but the statistical P value is given as reported.

Although not an effect of therapy, it was reported that there was a baseline statistically significant difference in fatigue levels between those patients who completed the study and those patients who withdrew before or soon after the start of the yoga course (mean baseline score for completers = 46.92 vs 26.15 for non-completers $P < 0.01$) showing that, at that point in time, completers had a higher level of fatigue.

Overall, women gained a favourable impression of the yoga therapy for both health and social reasons. The statistical analysis, conducted on a very low patient number, suggests that only a lag effect i.e. benefit the day after the yoga session was applicable to fatigue specifically. Across the whole study period there was no significant effect on this parameter.

Updated evidence (6.3)

Evidence summary

Two systematic reviews were identified to update the evidence on cancer related fatigue (CRF). Minton *et al.* (2007) conducted a thorough review on drug treatments for CRF but, for the purposes of answering this question, only the section on progestational steroids (including megestrol acetate) was relevant. This group of drugs was found not to have a significant effect on relieving CRF compared with placebo treatments and therefore was not recommended by the authors.

A high quality review of 28 RCTs on exercise regimes for the treatment of CRF (Cramp and Daniel, 2008) included a meta-analysis which showed a significant effect of exercise on reducing CRF. 16/28 trials were conducted on women with breast cancer and here too, a highly significant difference in fatigue scores between intervention and control groups was observed. The results

were based on post-test comparison since, in many cases there were no matched paired data i.e. pre- and post-test scores. A risk of selection bias may have overestimated the benefits of exercise to some extent. Since the review included all forms of exercise, a specific regime, intensity or duration could not be recommended.

References

Cramp F and Daniel J (2008) Exercise for the management of cancer-related fatigue in adults. Cochrane Database of Systematic Reviews: Reviews.

Minton O., Stone P., Richardson A., Sharpe M and Hotopf M (2008) Drug therapy for the management of cancer related fatigue. Cochrane Database of Systematic Reviews: Reviews.

Evidence tables

Question: What is the role of cancer related fatigue management in ABC?
Created by: Karen Francis on 02/08/2008

Minton <i>et al.</i> (2007)
Design: Systematic review of RCTs (Therapy). Evidence level: 1 Country: UK
Inclusion criteria: Included studies: RCTs that assessed drug therapy for the management of cancer related fatigue (CRF) compared with a placebo, usual care or a non-pharmacological intervention Included patients: Adult patients with a clinical diagnosis of cancer.
Exclusion criteria: None stated
Population: Number of patients = 587
Interventions: The review examined outcomes for four classes of drugs, psychostimulants, anti-depressants, haemopoetic growth factors and progestational steroids. Only the latter group comes broadly within the remit of the PICO question since this group included megestrol acetate. Four papers were reviewed on progestational steroids.
Outcomes: Differences in fatigue between intervention and control groups using self-reported measures or valid assessment tools or both. Adverse events.
Follow up: Follow-up in the individual trials had been up to 12 weeks.
Results: The combined studies were highly heterogeneous ($I^2 = 98\%$) and were therefore combined in a random-effects model for meta analysis. 3/4 studies used megestrol acetate and the fourth used medroxyprogesterone and the drug dosages were very variable. All but one study had recruited patients with a variety of tumour types. The number of breast cancer patients, if any, is unknown. Overall effect of combined studies: Z score = 0.78 (P = 0.44 NSD) and standardised mean difference = -0.49 (95%CI: -1.74-0.75)

Effect of megestrol acetate only:
 Z score = 0.67 (P = 0.5 NSD) and standardised mean difference = -0.66 (95%CI: -2.6-1.28)

Adverse events:
 OR = 0.80 (95%CI: 0.4-1.51) (NSD)

These results indicated that there was no significant difference between progestational steroids (or megestrol acetate alone) and placebo for the treatment of CRF.

General comments:

This paper describes a Cochrane review of drug therapy for the management of CRF. The review only provides limited evidence since the majority of drugs assessed were not relevant to this question and were for the purpose of treating co-morbidity such as depression or anaemia. Similarly the studies included patients at any point in the treatment pathway, including those undergoing curative therapy, those with advanced disease receiving palliative care and disease-free survivors.

The review was thorough and conducted in the usual way for a Cochrane review with respect to the databases used for searches, screening, study selection and assessment for suitable methods of randomisation, allocation and blinding by trial researchers. Wherever necessary, authors were contacted in order to obtain full trial data if not presented. Any differences between reviewers who were screening and assessing papers independently were resolved by consensus with other members of the Cochrane review group. Meta-analyses were performed with rigour.

Four papers were reviewed on progestational steroids which presented results from double blind or crossover placebo controlled RCTs. Patients in these trials were all off active treatment which they had undergone for a variety of tumour types. Follow-up had been up to 12 weeks. The review authors concluded that whilst the included papers were old (most recent being 1999) they were all of good quality but collectively, they provided no evidence for the continued use of this class of drugs in the treatment of CRF.

Cramp and Daniel (2008)

Design: Systematic review of RCTs (therapy). Evidence level: 1+
Country: UK

Inclusion criteria:

Included studies:
 RCTs that investigated the effect of exercise on cancer related fatigue (CRF) in adults.

Included patients:
 Adults of any age, regardless of gender, tumour type, tumour stage and type of cancer therapy. Participants may have been actually receiving treatment, be in long term follow-up or receiving palliative care.

Exclusion criteria:

None stated

Population:

Number of patients = 2083 (n=1172 with breast cancer). Age range: 39 to 69 years.

Interventions:

The review examined outcomes of exercise where the comparator was usual care, no exercise, or an alternative treatment or exercise regime. The intervention could take place in any setting, for individual or group participation.

13 studies were of home based and/or unsupervised exercise programmes, 16 were of supervised, institutional based exercise programmes (one study counted twice as it had data on both options). The programmes included walking (n=7) stationary cycling (n=4) strength training (n=3) resistance training (n=2) flexibility training (n=2) yoga (n=2) seated exercise (n=2) and aerobic exercise of various formats (n=13).

Outcomes:

To evaluate the effect of exercise on CRF both during and after cancer treatment. Subject to satisfactory data, to explore the effect of exercise on different types of cancer populations.

Outcomes of interest listed included: patient reported fatigue and also maintenance on follow-up, attrition, time spent exercising, measures of aerobic capacity, quality of life measures, anxiety, depression and self-efficacy.

Follow up:

Few studies reported long term follow-up.

Results:

The effect of exercise on all patients:

The combined studies were moderately heterogeneous overall ($I^2 = 46.7\%$) and a fixed effects model was used. The overall effect of exercise from post-test means (n=1662) was determined from 30 comparisons in 28 studies.

Z score = 4.57 ($P < 0.00001$) and standardised mean difference = -0.23 (95%CI: -0.33 to -0.013)

At the end of the intervention period exercise was statistically more effective than a control intervention.

The effect of exercise on breast cancer patients (n=977):

The combined studies were moderately heterogeneous for the breast cancer population ($I^2 = 48.9\%$) and a fixed effects model was used.

Post-test data were not available for 5/18 comparisons in 16 trials. Hence data from 13 trials were combined in a meta analysis (n=545 patients).

Z score = 5.36 ($P < 0.00001$) and standardised mean difference = -0.36 (95%CI: -0.49 to -0.23)

At the end of the intervention period exercise was statistically more effective than a control intervention.

General comments:

This paper describes a Cochrane review of the effect of exercise on CRF in adults. The studies included adults actually receiving cancer treatment or who were in long term follow-up or receiving palliative care.

The review was thorough and conducted in the usual way for a Cochrane review with respect to the databases used for searches, screening, study selection and assessment for suitable methods of randomisation, allocation and blinding by trial researchers. Wherever necessary, authors were contacted in order to obtain full trial data if not presented. Any differences between the two reviewers who were screening and assessing papers independently were resolved by consensus with a third reviewer. Meta-analyses were performed with rigour.

28 trials were included in this review of which 16 were of exercise regimes for patients with breast cancer. Analyses were presented for all studies and for this sub-group. The reviewers concluded that there was evidence to show that exercise is beneficial in the management of CRF

both during and after cancer treatment. A statistically significant benefit was also specifically shown for patients with breast cancer. The authors point out that the effects of any concurrent cancer treatment on these positive outcomes were yet to be determined. A specific type, intensity or timing of exercise is also not known.

The likelihood of bias may exist with respect to paper selection (English language papers only) and data selection (full trial data were not generally available in those studies for which a negative outcome was found for exercise). These could result in an over-estimation of the efficacy of exercise.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

6.4 Management of bone metastases

Short summary

The evidence base on the management of bone metastases included a systematic review (Sze *et al.*, 2002), a guideline (Warr *et al.*, 2002), five RCTs (Tripathy *et al.*, 2004, Hartsell *et al.*, 2005, Salazar *et al.*, 2001, Wardley *et al.*, 2005 and Rasmussen *et al.*, 1995), two comparative or cohort studies (Weinfurt *et al.*, 2004 and Pecherstorfer *et al.*, 2006) and six case series (Broos *et al.*, 1993, Gerszten *et al.*, 2005, Gristina *et al.*, 1983, Scarantino *et al.*, 1996, Borojevic *et al.*, 1999 and Durr *et al.*, 2002). There were no papers dealing specifically with solitary bone metastases, bone metastases as part of wider metastatic disease or rehabilitation.

Good evidence, including a treatment guideline, suggested that whilst bisphosphonates made little impact on overall survival, they could reduce pain and the occurrence of skeletal events. There was no comparative evidence to suggest that one bisphosphonate was better than others in any respect. A meta-analysis found no significant difference between oral clodronate and placebo or no treatment in terms of bone metastasis-free survival, disease-free survival or non-skeletal metastasis-free survival.

High quality evidence, including a systematic review with meta-analysis, demonstrated that single and multiple fractions of radiotherapy were equally effective at relieving pain. There was no strong evidence that single fractions resulted in a higher rate of subsequent fracture or spinal cord compression. An equivalence in outcomes between stereotactic radiosurgery as salvage therapy after disease progression with conventional radiotherapy and upfront external beam radiotherapy suggested a possible treatment for previously irradiated patients with few treatment options left.

The evidence on the use of radiotherapy to prevent skeletally related events was equivocal. Four observational studies provided limited evidence suggesting a potential role for surgery in giving pain relief.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with a solitary bone metastasis from breast cancer	<ul style="list-style-type: none"> Radiotherapy 	<ul style="list-style-type: none"> No radiotherapy Fractionation and dose 	Disease free/progression free/overall survival

POPULATION	INTERVENTION	COMPARISON	OUTCOME
<p>Patients with multiple bone metastases as the only apparent site of disease or as part of more widespread disease</p>	<ul style="list-style-type: none"> • Rehabilitation • Bisphosphonates • Bisphosphonates – all generations • Rehabilitation • Radiotherapy • Surgery, chemotherapy or endocrine therapy 	<ul style="list-style-type: none"> • No rehabilitation • No bisphosphonates • With each other, with different doses or with samarium • No rehabilitation • Different fractionation and dose or with no radiotherapy 	<p>Reduction in skeletal related events</p> <p>AND</p> <p>for all comparisons:</p> <ul style="list-style-type: none"> • Reduction in pain • Mobility/function • QoL • Cost effectiveness

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

The evidence base includes two systematic reviews (Spain & UK), a guideline (Canada), five RCTs (USA (n = 3), Denmark and UK), three comparative or cohort studies (USA & 2 European), ten case series (n = 8 European & n = 2 USA) and a phase II study (USA). The majority of papers recruited female patients with breast cancer and painful bone metastases but sometimes this group formed part of a larger patient population although data were usually reported separately. No papers dealt exclusively with patients having solitary bone metastases or having bone metastases as part of wider metastatic disease – such patients were sometimes included in the larger populations described in the studies below. Neither was there any papers addressing the question of rehabilitation.

Although the quality and reliability of papers is variable, six studies agree that strontium and samarium provide good pain relief and reduction in analgesia. Six studies provide variable strengths of evidence for radiotherapy (RT) and pain palliation for bone metastases suggesting that patients receiving single fraction RT are more likely to experience a higher re-treatment rate and incidence of fractures than those receiving multi-fraction RT but no more likely to gain pain relief or suffer more adverse events. No useful evidence was found that agreed an optimum dose or fractionation schedule however.

One systematic review of only two RCT failed to find a benefit of treatment with calcitonin for the alleviation of metastatic bone pain. Four papers described different surgical techniques, none of which were compared with any other treatment not were comparable with one another.

The largest evidence base was for bisphosphonate therapy: a guideline, two RCTs and two prospective studies suggesting overall that bisphosphonates reduce the incidence of skeletal

related events, make no impact on overall survival but improve the quality of life. There are inconsistent results on pain palliation.

Many of the outcomes in the poorer quality studies reported data as point estimates which cannot be regarded as having external validity i.e. applicability to the population as a whole, and cannot be compared across studies with any safety.

Strontium-89 (Sr-89) and samarium (Sm-153)

There were five papers relating to the use of strontium for pain palliation. Four were prospective case series and one was a self-styled RCT which has been appraised as a prospective comparative study (with subsequent lower grading). Three studies were exclusively concerned with breast cancer patients and two included such patients within a larger group. All patients had multiple painful bone metastases.

In all cases where reported, adverse events were related to haematological toxicity which was mild and responded to appropriate treatment.

Unfortunately, each of the five studies used different methods of assessing pain, including a modified Wisconsin test, a 10-point scale and other scoring systems using from 3-6 parameters each scoring up to 5 points. Obviously, this makes it impossible to combine data across studies and since the data are, in all but one paper, given as point estimates this would not be statistically sound anyway.

Most papers used bone scintigraphy to compare the degree of bone involvement at baseline with that post-treatment. One study measured tumour markers. Overall, no improvement in the degree of metastatic disease was observed leading to the conclusion by one author that strontium was not tumoricidal.

Sciuto *et al.* (2001) presented a comparison between single intravenous injections of Sr-89 (148 MBq) and Re-186 (1406 MBq) used in two 25-patient groups for pain palliation. Pain relief after Sr-89 was experienced in 84% patients within a median time of 21 days and for a median duration of 120 days. The data were given as point estimates and therefore must be viewed with caution. Patients receiving Rhenium did not have a significant advantage in the degree of pain relief or its duration but the treatment worked much more quickly as the median time to relief was only 4 days. This study was presented by the authors as a RCT but since there was no mention of randomisation, allocation, blinding etc is perhaps more correctly assessed as a prospective comparative study.

Baziotis *et al.* (1998) presented a case series of 64 patients who received a 150 MBq single bolus injection of Sr-89 for pain palliation. Pain relief occurred in 81% of patients within 10-20 days but, again, data are only point estimates and therefore not comparable with those from other studies. Berna *et al.* (1995) treated 15 patients with a single injection of between 118-148 MBq of Sr-89 and recorded pain relief in 47% patients which lasted from 3 to 7 months.

Kasalicky and Kraiska (1998) treated 118 patients suffering with painful bone metastases from a variety of primary cancers, including 23 with breast cancer. A 'substantial' improvement in pain relief was achieved by 43.5% of breast cancer patients with a mean duration of the first dose of 3.08 ± 0.48 months. In 13% of these patients the improvement was graded as 'dramatic' and for the remaining 45% 'mild'. Analgesia was reduced by up to 45% in 15/23 (65%) patients and 20/23 (87%) patients had improved mobility.

Pons *et al.* (1997) presented a small case series of 76 prostate (n = 50) and breast (n = 26) cancer patients who had received a single bolus injection of 148 MBq of Sr-89 for pain palliation. A good response was recorded in 62% patients, taking into account both pain relief and a decrease in analgesia use. The improvement occurred in the 2nd or 3rd week after treatment.

Taken together, these studies provide fairly weak evidence of the efficacy of strontium in pain palliation, primarily because the majority of studies have no comparators with which to measure strontium against. However, all authors offered the opinion that Sr-89 provides good pain relief with few adverse effects for patients that have multiple painful bony metastases. The most recent paper was 2001. More up-to-date evidence was not identified.

The other radiopharmaceutical commonly used in breast cancer patients is samarium-153. There was only one retrospective case series (Coronado *et al.* 2006) which reported treatment outcomes for 64 patients, of which only 28 had MBC with bone metastases. The dose of 2479 MBq Sm-153 was given in a single bolus injection although some patients received a second treatment a few months later. Pain relief was reported by 82% of evaluable patients with a 55% reduction in analgesia use. The improvement in pain was apparent after a median time of 7 days and persisted for a mean of 3 months. One patient suffered grade 4 haematological toxicity.

Radiotherapy (RT)

There were six papers relating to radiotherapy for bone metastases including a Cochrane review (Sze *et al.*, 2002), three RCTs (Hartsell *et al.*, 2005; Salazar *et al.*, 2001 and Rasmussen *et al.*, 1995) and two observational studies (Scarantino *et al.*, 1996 and Borojevic *et al.*, 1999).

Three of these papers dealt solely with breast cancer patients (Sze *et al.*, 2002; Rasmussen *et al.*, 1995 and Borojevic *et al.*, 1999) whereas the other three studies were concerned with a larger target population including prostate and other primary cancers. In all but one (Hartsell *et al.*, 2005) study, all patients had multiple and painful bone metastases. One paper specified bone-only disease whereas the other papers made no reference to the presence or otherwise of visceral disease. There were no publications that dealt only with solitary bone metastases.

The best quality evidence relates to the comparison of single and multiple-fraction RT. Four papers relating to sixteen different and largely non-overlapping fractionation dosages and regimes are considerably less valuable in terms of presentation, content and patient number (a total of 716 patients).

A high quality Cochrane systematic review (Sze *et al.*, 2002) analysed data from 11 RCTs of single fraction (8-10 Gy x 1) versus multiple fraction (from 5 Gy x3 to 3 Gy x 10) RT. Six outcomes were summarised: overall pain response, complete pain response, re-treatment rate, pathological fracture rate, spinal cord compression and adverse events. Of these, only re-treatment rate (21.5 vs 7.4%) and incidence of pathological fractures (3 vs 1.6% P = 0.03) were significantly higher in the single fraction RT group. All other outcomes were not significantly different between treatments. A total of 3,435 patients were included in these analyses of which 39.3% had metastatic breast cancer.

A more recent study by Hartsell *et al.* (2005) also offered good evidence from a RCT of 898 patients (of which 50% had breast cancer) randomised to received either single fraction (8 Gy x 1) or multiple fraction (3 Gy x 10) RT. There was no significant difference in median overall survival (9.1 months single fraction versus 9.5 months multi-fraction; P = 0.82) or complete pain relief (15% single fraction vs 18% multi-fraction). A sub-group of patients with a solitary bone metastasis experienced similar responses to pain of 18% (single fraction) vs 21% (multi-fraction). The rate of re-treatment overall was significantly higher for patients treated with single fraction RT (18% vs 9%; P < 0.001) but the rate of pathological fractures was not significantly different (4% vs 5%), which is a different result from that obtained in the systematic review (Sze *et al.* 2002) and possibly due to the presence of prostate cancer patients in this study, the results for which are not separately reported. A short abstract detailing the quality of life data is appended to the evidence.

Rasmussen *et al.* (1995) reported a poor quality RCT of 217 patients randomised to two multi-fraction regimes (3 Gy x 10 over 10-12 days vs 5 Gy x 3 over 8-9 days). There was no significant difference in overall survival, pain relief, activity level or analgesia post-treatment between the two

doses. The data were very poorly presented (use of approximations, percentages, no confidence intervals or ranges). Additionally there were no details of the randomisation and allocation processes although some of the outcomes were assessed by investigators blinded to treatment.

Borojevic *et al.* (1999) presented a complex multi-arm prospective case series of 386 patients, unequally divided into six groups by RT regime (short, medium or long intervals between treatments with variable dosages from 14 Gy in 2 fractions in 2 days to 40 Gy in 20 fractions in 28 days). The shorter regimes gave significant improvements in efficacy between the first (baseline) and second (after 2 months) assessments and median overall survival was 31 months. Data were poorly presented, without confidence intervals and there inadequate explanations of how some of the test statistics were derived. The variation in patient numbers per group makes comparisons between treatments less sound. Some patients appear to have had bone-only disease since separate Kaplan-Meier survival data are presented for these patients (from the graph, median overall survival exceeds 60 months). Additionally, some patients appear to have had more widespread visceral disease but this sub-group is not separately reported.

Salazar *et al.* (2001) also presented data on variable dose and treatment interval hemi-body RT. 156 patients, with various primary cancers but all with painful bony metastases, were randomised by method unknown into 3 treatment groups (15 Gy in 5 fractions over 5 days, 8 Gy in 2 fractions over 1 day and 12 Gy in 4 fractions over 2 days). Data for patients with breast cancer were separately reported. Some patients (8%) had additional visceral metastases but these may not have been breast cancer patients. Median overall survival for MBC patients across all treatments = 203 days (range: 198-214); Progression-free survival = 144 days (range: 134-153) and quality of life score was 70%. By treatment regime for all patients, the 15 Gy x 5 dose gave superior pain relief ($P = 0.016$), median overall survival ($P = 0.023$) and median progression-free survival ($P = 0.034$) compared with other doses. Quality of life was also said to be better with the 15 Gy regime. The data are given as percentages per total population and are presented without confidence intervals. Toxicity was reported by region irradiated so that in the upper body, the highest number of adverse events (23% of patients) occurred at the 8 Gy x 2 dose but in the lower body irradiation the 12 Gy x 4 doses caused more patients (12%) side effects.

Scarantino *et al.* (1996) presented a multi-fraction hemi-body RT regime case series. 142 patients received one of five different treatment protocols with doses ranging from 10 Gy to 20 Gy at a daily dose of 2.5 Gy. Since all patients had either breast or prostate cancer and there were 41 females in the study, it would be reasonable to assume that at least 29% of patients had MBC. This paper was predominantly a dose-finding study and was underpowered for intra-group comparison but was included here only because of the reporting of survival data. The 1yr overall survival rate was 41% at lower doses (10-12.5 Gy) and 44% at higher doses (15-17.5 Gy). The initial survival advantage of higher dosage was lost 2yrs after treatment but the authors concluded that 17.5 Gy in 2.5 Gy is a safe and effective dose in the short term. The majority of adverse events were haematological in nature and included anaemia, leukopenia and thrombocytopenia.

Endocrine therapy

Only one relevant paper was identified: a Cochrane systematic review of calcitonin for metastatic bone pain (Martinez-Zapata *et al.*, 2006). This evidence comprised only 2 RCTs, both of which related to breast cancer, and concluded from these that calcitonin did not help in the control of bone pain or for improving overall survival or quality of life. This review was rigorously performed on a relatively small ($n = 90$) number of patients.

Surgery

Only three retrospective case series (Broos *et al.*, 1993; Gristina *et al.*, 1983 and Durr *et al.*, 2002) and one prospective case series (Gerszten *et al.*, 2005) were identified that described any form of surgery for bone metastases from breast cancer.

Broos *et al.* (1993) provided very weak evidence on a case series of 77 fractures in 65 patients, 75% of whom had breast cancer. The techniques varied: either osteosynthesis (including as prophylaxis for patients with impending fractures) or endoprosthesis. Good pain relief was obtained for 78% of patients and the mean survival for breast cancer patients was 13 months (no confidence intervals). The data are weak and largely anecdotal.

Gerszten *et al.* (2005) tested the Cyber Knife Image-Guided Radiosurgery System in the treatment of 50 patients with spinal breast metastases, 32 of which were solitary. 96% of patients reported long term improvement in pain compared with pre-operative values over a follow-up period of 16 months. Whilst a small case series and of little evidential value in that respect, this technique seems to have been effective and with no adverse effects. Unfortunately, no other reports linking this methodology with treatment for breast cancer metastases were identified.

Durr *et al.* (2002) reported outcomes on a series of 70 patients that had received one of ten different surgical procedures for bone metastases either in the spine, femur or pelvis. Post-surgical complication occurred in 14 patients and included pulmonary dysfunction, cardiac insufficiency, neurological impairment, bleeding, multi-organ failure, infection, thromboembolus and surgical failure. No patients had tumour progression or recurrence at the surgical site. Of patients with solitary metastases, 12/19 died from progressive disease, 3 had ongoing disease and 4 had disease-free survival for longer than 5 year. 17/19 patients with bone-only disease died from progressive disease and 29/32 with widespread involvement also died of disease progression and the remaining patients were alive but with disease progression. Overall, survival rate was 7% after 10 years and 13% after 5 years with the most predictive factor being the degree of disease (multiple bone involvement and visceral spread) at the time of surgery.

Gristina *et al.* (1983) presented a retrospective review of 25 breast cancer patients with bone metastases who had open reduction, internal fixation with a plastic polymer and then radiotherapy. Surgery was performed on five sites including hip, arm and leg and as prophylaxis for impending fractures. The mean overall survival was 19.9 months and at 7 years the survival rate was ~25%. Pain relief was graded as 'good' by 74% of the patients.

None of these papers offers strong evidence towards any surgical procedure – all are case series without comparators and relate to different surgical approaches through a 22-year period from 1983 to 2005.

Bisphosphonates

The largest evidence base for the treatment of bone metastases from breast cancer relates to bisphosphonates. There is one high quality guideline, two RCTs (one of high quality and the other of moderate quality) and two prospective studies.

The guideline (Warr *et al.*, 2002) was produced by Cancer Care Ontario and has been appraised using the AGREE instrument – the work was judged to be of high quality. The original 2002 document included analysis of a Cochrane systematic review, 28 RCTs and two other evidence-based guidelines (ASCO and SIGN). The 2004 update added further data from meetings and papers that were incomplete at the time of the first publication. Studies included any bisphosphonate (clodronate, pamidronate, ibandronate or zoledronate) compared with another bisphosphonate, with placebo or no treatment; different routes of administration or different dosages. The findings were that oral clodronate and i.v. pamidronate significantly reduced the incidence of skeletal related events (SREs) and bone pain. Direct comparisons found that 4 mg zoledronate was equivalent to 90 mg i.v. pamidronate given every 3-4 weeks. Overall, the conclusions were that bisphosphonates did not improve overall survival but reduced the incidence of SREs and pain.

Tripathy *et al.* (2004) presented a high quality RCT of 435 patients, randomised to receive oral ibandronate at one of two different doses (20 mg or 50 mg daily) or placebo. Patient groups were

well matched in most characteristics and areas of variation were identified. After treatment, the relative risk of having a SRE was significantly lower in the two ibandronate arms compared with placebo (RR = 0.61). The pain scores were not significantly different in patients treated with ibandronate (either dose) and those on placebo although the analgesia scores were significantly higher in the placebo group compared with the 20 mg ibandronate group (P = 0.006) but not significantly different from the 50 mg ibandronate group. There was a very high drop-out rate (~60%), evenly spread between the three arms, and 18 patients were lost to follow-up.

Wardley *et al.* (2005) produced a lower quality study of 101 (from an original recruitment of 127) patients who took part in a randomised, open label crossover trial which evaluated the advantage of community versus hospital treatment with 4 mg i.v. zoledronate. The primary outcome was efficacy and quality of life, including patient satisfaction. The numbers were rather low for such a trial, confounded by a drop-out of 17 patients who did not complete treatment and 8 deaths during the study period. The evaluation of bone pain (BPI) resulted in a statistic derived from a number of contributing factors including pain assessment, general wellbeing, mobility, sleep etc. Although some of the individual elements were improved for the overall population the composite BPI score was not significantly different between baseline and post-treatment. (P = 0.077). However, patients in the community setting had a significantly higher BPI score than patients treated in hospital (P = 0.008).

Quality of life was measured by the EORTC QLQ-30 scale: the global health score is a composite derived from a number of functional elements. The global score significantly improved for all patients treated with zoledronate compared with baseline values (P = 0.013) and for patients in the community setting there was a significant improvement in physical (P = 0.018), emotional (P = 0.001) and social (P = 0.026) functioning compared with patients treated in the hospital setting. The breast module (BR23) also revealed significant improvements with zoledronate treatment against placebo, some advantages of which occurred in either of the treatment arms. Overall, patients were satisfied with the zoledronate treatment but more so in the community setting. Adverse events were documented but only 2 were treatment related.

A prospective cohort study (Weinfurt *et al.*, 2004) compared two doses of i.v. zoledronate (4 mg or 8 mg) with i.v. pamidronate (90 mg) in 1124 patients. Unfortunately, this paper was focused more on the complex modelling of health-related quality of life scores than on the data per se. The original RCT included patients with myeloma and breast cancer but the data have been selected for the latter group only. 63% patients in the 4 mg zoledronate group and 60% in each of the other two arms completed the course of treatment (1 year). The authors concluded from their data that patients on zoledronate experienced a gradual increase in physical, functional and emotional well-being. Their QOL outcome was adversely affected if they had experienced a SRE before commencing treatment which strengthened the authors' belief that successful treatment of SREs would contribute to an improved QOL.

Finally, Pecherstorfer *et al.* (2006) presented data from a group of 62 breast cancer patients who participated in a post-RCT study which had originally randomised them to receive either a 2 mg or 6 mg i.v. dose of ibandronate or placebo for 96 weeks. Since in the original trial, 6 mg ibandronate proved to be of greater efficacy than the lower dose treatment or to placebo, the 6 mg dose was chosen for this extension study and was administered for a further 96 weeks. Data was given for the two treatment groups: those patients who had received 6 mg ibandronate and continued on this dose ('6/6' n = 46) or those patients who had received placebo and then received 6 mg ibandronate ('P/6' n = 16). The primary outcomes were adverse events – the data are presented as percentages and appear not to have been statistically analysed. Treatment-related events and those leading to death appear to be higher in the 6/6 arm whereas serious adverse events, including those leading to withdrawal appear to have occurred more in the P/6 group. This reporting quality of this study is poor but the authors claim long term safety for this treatment.

Together, these studies offer evidence that varies in quality but confirms that bisphosphonates reduce the incidence of skeletally related events, improve the quality of life (perhaps more so in the community setting). There are mixed results on pain reduction; the strongest class of evidence suggests that bisphosphonate treatment can provide an improvement in pain relief but other, less highly graded, studies indicate no effect. There is also good evidence to suggest that bisphosphonates make no impact on overall survival.

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Evidence tables

Question: The management of bone metastases
 Created by: Karen Francis on 05/12/2006

Martinez-Zapata <i>et al.</i> (2006)
Design: Systematic review of RCTs (therapy), evidence level: 1 Country: Spain
Inclusion criteria: Randomised double blind clinical trials of patients with metastatic bone pain treated with calcitonin where the major outcomes measure was pain assessed at 4 weeks or longer. Patients had bone pain metastatic pain caused by any primary tumour diagnosed by CT, bone gammagraphy, NMRI or other radiographic process.
Exclusion criteria: Previous bisphosphonate therapy Studies where patients were assessed < 4 weeks after treatment
Population: Number of patients = 90.
Interventions: Calcitonin plus rescue medication versus placebo plus a rescue medication or any comparison between different models and intervention doses.
Outcomes: Primary: to assess the effectiveness of calcitonin in controlling metastatic bone pain Secondary: in reducing bone complications (hypercalcaemia, fractures and nerve compression) in patients with bone metastases. Quality of life, adverse events, length of time of any improvement.
Follow up: There were a total of 4 patients lost to follow-up.
Results: Only 2 RCTs met the inclusion criteria with a total of 90 women with breast cancer and painful bone metastases.

Of the two small studies included in the review, one study showed a non-significant effect of calcitonin in the number of patients with total pain reduction (RR = 2.50 95%CI: 0.55-1.41).

The second study provided no evidence that calcitonin reduced analgesia consumption (RR = 1.05 95%CI: 0.90-1.21) in patients with painful bone metastases.

There was no evidence that calcitonin was effective in controlling complications due to bone metastases; for improving quality of life; or patients' survival. Although not statistically significant, a greater number of adverse effects were observed in the groups given calcitonin in the two included studies (RR = 3.35 95%CI: 0.72-15.66).

General comments:

Authors' summary: "The limited evidence currently available does not support the use of calcitonin to control pain from bone metastases. Since the last version of this review, none of the new relevant studies have provided additional information on this treatment, in contrast to other therapeutic approaches that should be considered".

This systematic review was rigorously performed on a very small amount of data. Meta analyses were presented and the evidence was well reviewed and summarised.

Sze et al. (2002)
Design: Systematic review of RCTs (therapy), evidence level: 1++ Country: UK
Inclusion criteria: Only published RCTs or abstracts were included and there was no contact with authors in the event of the need for clarification or verification of data. Patients had painful bone metastases from any primary tumour.
Exclusion criteria: Studies relating to the use of radioisotopes or drugs.
Population: Number of patients = 3,435.
Interventions: Single fraction external radiotherapy (RT) versus multi-fractionated external RT. Single fraction doses varied from 8-10 Gy and the schedules of multi-fraction doses ranged from 5 Gy in 3 fractions (5 Gy x 3) to 3 Gy in 10 fractions (3 Gy x 10).
Outcomes: Efficacy in treatment of pain and prevention of fractures: complete pain response, re-treatment rate, pathological fracture rate, spinal cord compression and side effects.
Follow up: Drop-out rates ranged from 0-69% in the completion of pain evaluations.
Results: 11 studies were included with a total of 3,435 patients. Overall pain response (n = 3,435): All studies reported this outcome. Overall pain responses were similar for single fraction RT (60%) versus multi fraction RT (59%). The pooled odds ratio was 1.03 (95%CI: 0.89-1.19). The test statistic for heterogeneity was P = 0.7 (nsd).

Complete pain response (n = 2,876):

7 studies reported this outcome. The response rate for single fraction RT was 34% compared with 32% for multi-fraction RT with a pooled odds ratio of 1.11 (95%CI: 0.94-1.3). The test statistic for heterogeneity was 0.81 (nsd).

Re-treatment rate (n = 2,476):

5 studies reported this outcome. There were more re-treatments after single fraction RT (21.5%) than multi-fraction RT (7.4%) (overall odds ratio = 3.44 (95%CI: 2.67-4.43). The test statistic for heterogeneity was 0.18 (nsd).

Pathological fracture rate (n = 2,476):

5 studies reported this outcome. There were more pathological fractures with single fraction RT (3%) compared with multi-fraction RT (1.6%) (P = 0.03). The test statistic for heterogeneity was 0.31 (nsd) but the individual odds ratio were variable. The overall odds ratio = 1.82 (95%CI: 1.06-3.11).

Spinal cord compression (n = 2,206):

3 studies reported this outcome. There was no significant difference between the two treatment modalities in the occurrence rate for spinal cord compression. Single fraction RT rate was 1.9% versus 1.4% for multi-fraction RT. The test statistic for heterogeneity was 0.93 (nsd). As only 739 of the 2,206 patients in this group had spinal metastases the analysis was repeated for this subgroup with similar results.

Side effects:

The commonest side effects reported were nausea and vomiting, of equal severity in single and multi-fraction RT arms.

General comments:

This Cochrane review examined the issue of single versus multi-fraction radiotherapy in the relief of pain and the prevention of pathological fractures from bone metastases. The study participants had a variety of primary cancers, of which 39.3% had breast cancer.

Electronic search was made of Medline, Embase, CancerLit and the controlled trials registry of the Cochrane Library. The search terms are given in full. Additional material was sought in reference lists of the selected papers and relevant journals and conference proceedings were hand searched. Study selection was undertaken by two researchers.

Studies were graded using the Jadad method. Excluding the element for blinding, which is not feasible with RT studies, points (either 1 or 0) were awarded for randomisation, reporting of randomisation and description of drop-out and withdrawal - only 1 study scored 3 points.

Data for each outcome were thoroughly described and had accompanying Forrest plots.

Pain assessment methodology varied between RCTs and there was a high drop-out in this category, due to death or ill health which precluded filling in the assessment forms. The authors comment that this could be a source of bias.

The higher rate of re-treatment and fractures for single fraction RT may undermine the advantage of this option.

Hartsell *et al.* (2005)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United States

<p>Inclusion criteria: Histologically proven breast or prostate cancer Radiographic evidence of bone metastases (up to 3 sites) Pain associated with bone metastases Minimum age 18yrs Written informed consent Karnofsky performance status (KPS) \geq 40 Estimated life expectancy > 3 months</p>
<p>Exclusion criteria: New systemic therapy within 30 days of study entry Prior RT therapy for pain in the treatment area or palliative surgery or planned bone fixation Clinical or radiographic evidence of spinal cord compression</p>
<p>Population: Number of patients = 898, age range 31 to 92 years, mean age = 65 years, median age = 67 years.</p>
<p>Interventions: Group 1: 8 Gy x 1 (single dose) Group 2: 3 Gy x 10 (in 2 weeks)</p>
<p>Outcomes: Comparison of the degree, frequency and duration of pain and narcotic relief between treatment arms. Pain was assessed by the 'worst pain score' from the Brief Pain Inventory.</p> <p>Responses after three months were rated as: complete (CR) if no pain, partial (PR) if the pain score was at least 2 points lower than baseline, stable disease (SD) if there was a 1 point change in score either way and progression (P) if the pain score was at least 2 points higher than baseline.</p> <p>Incidence of pathologic fracture within the treatment field for 8 Gy x 1 compared to 3 Gy x 10.</p> <p>Overall survival.</p>
<p>Follow up: Baseline assessment included history and physical examination, KPS, radiography, completed Brief Pain Inventory and Functional Assessment of Cancer Therapy (FACT) and Health Utilities Index III.</p> <p>The questionnaires were repeated after 2 and 4 weeks and at 2, 3, 6, 9, 12, 18, 24, 30, 36, 48 and 60 months)</p> <p>128 patients were lost to follow-up, all due to death (group 1 = 63, group 2 = 65).</p> <p>Median follow-up for patients with reported toxicity was 7.6 months (range: 0.2-49).</p>
<p>Results: Patient characteristics were listed and were stated to be similar between treatment arms (no statistics).</p> <p>Survival: Median OS group 1 = 9.1 months Median OS group 2 = 9.5 months (P = 0.82) Overall survival at 1 year group 1 = 41%</p>

Overall survival at 2 year group 1 = 22%
Overall survival at 1 year group 2 = 42%
Overall survival at 2 year group 2 = 22%

Adverse events:

There were 70 adverse events (grades 2-4) in group 2 patients compared with 42 events in group 1 (% difference = 7% 95%CI: 3-12 P = 0.002).

Two patients in group 2 had grade 4 acute toxicities (emesis and neutropenia) and 2 patients in each treatment group had grade 3 late toxicity (CNS, haematological or 'other').

Pain relief:

Although 845 patients completed the baseline BPI, only 573 (67.8%) of these also completed the assessment at 3 months (n = 288 in group 1 and n = 285 in group 2).

Overall CR = 93 (17%)
Overall PR = 280 (49%)
ORR = 375/573 (66%)
P = 55 (10%)

CR group 1 = 44 (15%)
CR group 2 = 51 (18%)
PR group 1 = 143 (50%)
PR group 2 = 137 (48%)

For patients treated for a solitary metastasis:

CR group 1 = 29 (18%) n = 165
PR group 1 = 85 (52%)
CR group 2 = 32 (21%) n = 156
PR group 2 = 79 (51%)

At 3 months, 33% patients overall no longer required analgesia.

There was no difference in pain relief between the two arms when stratified by number of painful sites, weight-bearing status, pre-treatment pain score or bisphosphonate use (full data given).

Incidence of pathological fractures within the treatment site:

Group 1 = 5%
Group 2 = 4%

Rates of re-treatment at 3 years:

Group 1 = 76/449 (18%)
Group 2 = 33/432 (9%) P < 0.001

Note: the following data appeared in a meeting abstract relating to QOL (Prospective Health-Related Quality of Life Valuations (Utilities) of 8 Gy in 1 Fraction vs 30 Gy in 10 Fractions for Palliation of Painful Bone Metastases: Preliminary Results of RTOG 97-14 (Bruner DW, ASTRO 2004):

"Based on the data, there was no difference in overall HUI-III-HRQL scores between the two treatment arms at baseline or at 3 mos. Utility scores increased significantly from baseline to 3 mos. for each of the treatment arms. The increased utility of changes in emotion on the 30 Gy arm may indicate a benefit from increased social support gained with longer treatment time. Cognition decreased equally on both arms congruent with the

literature on metastasis".
<p>General comments: This paper presents a RCT of two regimes of RT for painful bone metastases secondary to prostate or breast cancer. The greater percentage (50.4%) were patients with MBC. 949 participants were recruited between 1998 and 2001 and of these 898 were randomised (reasons for ineligibility were detailed).</p> <p>Treatment allocation was by the permuted block design with balance maintained between institutions and stratification by the number of sites, treatment site, initial worst pain score and use of bisphosphonates. Overall, the hypotheses and statistical methodology was well described and appropriate. Blinding was not feasible since patients were aware of treatment and the responses were subjectively assessed by them and not by an objective operator.</p> <p>The authors state that external beam radiation therapy was very effective in providing pain relief, with complete or partial improvement in pain seen in 66% of patients. Pain and narcotic relief was equivalent for both 3 Gy x 10 fractions and 8 Gy x 1 fractions. At 3 months follow-up, there was no difference between the two treatment arms, regardless of stratification. Treatment was well tolerated with few adverse effects.</p> <p>Survival data were given as point estimates without confidence intervals.</p> <p>The scores for the 3 month BPI questionnaire could only be collected for 68% of the population - death or illness prevented 32% of patients from completing the forms.</p>

Tripathy <i>et al.</i> (2004)
<p>Design: Randomized controlled trial (therapy), evidence level: 1+ Country: United States</p>
<p>Inclusion criteria: Women with histologically confirmed BC with radiologically confirmed bone metastases WHO performance status = 0-2 Minimum age = 18 years Written informed consent</p>
<p>Exclusion criteria: Bisphosphonates or gallium nitrate within 6 months Life expectancy < 60 weeks Hyper- or hypo-calcaemia Serum creatinine > 3 mg per dl Paget's disease of bone Primary hyperparathyroidism Known liver or brain metastases Treatment with aminoglycoside antibiotics within past 4 weeks</p>
<p>Population: Number of patients = 435, age range 29 to 92 years, median age = 57 years.</p>
<p>Interventions: Patients were randomised to receive either: group A: oral ibandronate 20 mg daily (n =144) group B: oral ibandronate 50 mg daily (n =148) or Placebo (n = 143) for up to 96 weeks, with instructions on self administration. Drug use was monitored by return of packaging.</p>

Outcomes:

Primary outcome: Skeletal morbidity (SMPR) broadly defined as the number of 12-week periods with new SREs (vertebral or non-vertebral fractures, bone RT or bone surgery) divided by the number of periods on the study.

Bone pain. Bone pain was rated on a self assessment scale from 0 (none) - 4 (intolerable). Analgesia use was also scaled from 0 (none) - 6 (opiates \geq 100 mg morphine or equivalent daily).

Time to first new bone event

Relative risk (RR) of experiencing a SRE

Adverse events

Follow up:

Baseline and X-rays were repeated at 4-weekly intervals together with assessment for fractures, bone pain and analgesia consumption.

Adverse events were recorded throughout the study.

Follow-up included collecting post-withdrawal data regarding safety and efficacy up to the point of death or last scheduled visit for those patients who left the trial early.

In the placebo group, a total of 89 patients left the trial, also 89 in group A and 85 in group B. The most common reasons for withdrawal from the study in all groups were cancer progression, death or personal reasons. None were related to the oral administration e.g. difficulty in taking the tablets.

A total of 18 patients were lost to follow-up: 4 in group A, 8 in group B and 6 in the placebo group.

Results:

Efficacy:

Patients with active treatment had a significant improvement in mean SMPR compared with patients on placebo. This was mainly due to the significant reduction in patients requiring RT ($P = 0.004$) whilst receiving ibandronate. Other components of SMPR were not significantly different between groups.

The RR of having SREs was significantly lower with both group A (RR = 0.62, $P = 0.009$) and group B (RR = 0.61, $P = 0.005$) compared with placebo.

Time to the 1st new bone event after randomisation was 48 weeks for the placebo group which, whilst shorter, was not significantly different from either group A (76 weeks) or group B (54 weeks).

From baseline to study end point, bone pain scores increased in the placebo group (+0.21) and group B (+0.03) but decreased for group A (-0.06) - these differences were not statistically significant.

From baseline to study endpoint, the mean analgesia score was higher in the placebo group (0.96) compared with group A (0.43, $P = 0.006$) or group B (0.73, nsd).

Adverse events:

Treatment related events (nausea, hypocalcaemia and abdominal pain) were more common in group A (26.4%) and group B (27.9%) compared with placebo (21.7%). Approximately 10% of ibandronate treated patients experienced upper GI tract problems and 6 patients (1 placebo) withdrew because of oesophagitis or dyspepsia. Renal effects were not significantly different

<p>between groups and 1 patient (group B) withdrew because of azotemia.</p>
<p>General comments: This paper presents data from a large (68) multi-centre (6 countries) randomised, double blind, placebo controlled trial of two doses of ibandronate versus placebo.</p> <p>The authors stated 'randomisation was according to a pre-determined randomisation list based on block randomisation'. This is appropriate to the smaller trial and ensures an equal number of participants in each group.</p> <p>Authors identified differences in baseline characteristics between study groups including WHO status and time since diagnosis.</p> <p>An appropriate regression analysis was performed to determine the risk of developing a SRE during the study period whilst adjusting for baseline differences in the three study groups.</p> <p>Efficacy data were analysed on an intention to treat principle whilst safety included all randomised patients who had received at least one treatment and at least one follow-up assessment.</p> <p>This is a good quality study (MF4434) which reports the effectiveness of self administered, oral ibandronate at reducing pain and the incidence of SREs, mainly through a reduction in the need for RT. The only feasible source of distortion was the high drop-out rate (~60%).</p>

<p>Rasmussen <i>et al.</i> (1995)</p>
<p>Design: Randomized controlled trial (prognosis), evidence level: 1- Country: Denmark</p>
<p>Inclusion criteria: Breast cancer Painful osteolytic lesions in spine, sternum, pelvis or extremities Oral consent</p>
<p>Exclusion criteria: Medullary compression from vertebral metastases Fracture in bone metastases prior to irradiation (other than compression fractures).</p>
<p>Population: Number of patients = 217, age range 35 to 84 years, median age = 59 years.</p>
<p>Interventions: Group A: 30 Gy in 10 fractions over 10-12 days Group B: 15 Gy in 3 fractions over 8-9 days</p>
<p>Outcomes: Efficacy of treatment was determined by means of pain assessment, radiological evaluation and noting of side effects between the two regimes.</p> <p>Patients rated pain on a four point scale, pain relief on a five point scale and level of activity on a four point scale.</p> <p>Definition of responses: Complete response (CR) = complete disappearance of lesion with new bone growth Partial response (PR) = decreased size of lytic focus or appearance of sclerosis in the or around the lesion Mixed response (MR) = Increase in number and/or size of lesions with appearance of sclerosis in</p>

previous foci
Progressive disease (PD) = increase in size or number of foci within the radiated field.

Follow up:

At baseline and at 1, 3, 6 and 12 month intervals analgesic medication was registered and the level of pain, pain reduction and activity limitations in the preceding 7 days were evaluated by physicians blinded to treatment allocation.

At the same time points as other evaluations, X-ray studies of bone metastases were undertaken and were evaluated retrospectively by a radiologist. Additionally, patients were interviewed about possible side effects.

Results:

217 patients were randomised but 14 died before treatment and another 3 patients did not complete the treatment. 200 patients were evaluated for response.

Median OS Group A = 12 months
Median OS Group B = 11 months

There was no significant difference in the efficacy of treatment for pain relief between groups A and B and both achieved a significant pain reduction after 1 month ($P < 0.001$). Thereafter, pain relief persisted but did not improve.

Level of activity improved in both groups ($P < 0.01$) from approx. 80% (severe reduction) and 63% (moderate reduction) to approx. 40% after 1 month and persisting thereafter. There were no significant differences in analgesia use between the groups at any time.

The response rate did not differ between the two groups. The number of patients experiencing CR or PR improved significantly from 1-3 months after treatment ($P = 0.001$) and remained stable thereafter.

New metastases developed in Group A ($n = 14$) and B ($n = 13$). 150 patients were evaluated radiologically and the tumour type made no significant difference to response which ranged from 70-78% (data was not shown).

Side effects were not significantly different between groups A and B. The most common symptoms were nausea and diarrhoea.

General comments:

This paper details what has been described by the authors as a randomised trial although there are no details of allocation given. Some of the parameters were assessed blind to treatment.

The two groups were stated to be equivalent at baseline in terms of tumour localisation, number of evaluable patients, level of pain and analgesic consumption but group A patients had a greater tendency towards limited activity at the start of the study.

Many of the results are more anecdotal than numerical with the use of approximations, point estimates (no confidence intervals or ranges) and probability estimates without data.

Unfortunately this is rather weak evidence. The authors state that there were no significant differences between regimes in any aspect and that therefore the 15 Gy x 3 regimes would be a suitable alternative to the accepted standard practice of the time i.e. 30 Gy x 10.

Salazar *et al.* (2001)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: United States
Inclusion criteria: Pain or narcotic score ≥ 4 Age < 80 years ECOG status = 1-4 Pathologically confirmed cancer Life expectancy > 2 months Adequate haematological and renal function (details given)
Exclusion criteria: Active cardiac or renal disease History of large volume radiation to the upper body
Population: Number of patients = 156.
Interventions: Schedule A: 15 Gy x 5 fractions in 5 days (MBC = 27) Schedule B: 8 Gy x 2 fractions in 1 day (MBC = 25) Schedule C: 12 Gy x 4 fractions in 2 days (MBC = 20) Three different fields were irradiated: upper half of the body (UHBI, n = 68 overall), mid-section (MBI, n = 9 overall) and lower half of the body (LHBI, n = 79 overall). The fields are thoroughly described in the text. None of the schedules required protection for kidney or liver but lungs were protected during the last fraction in schedules A and C.
Outcomes: Pain scores were obtained as the product of pain severity (none = 0, mild = 1, moderate = 2, severe = 3) and pain frequency (none = 0, occasional = 1, intermittent = 2 or constant = 3). Narcotic score was similarly obtained as the product of severity (none = 0, analgesic = 1, mild narcotic = 2 or strong narcotic = 3) and frequency (none = 0, < x1 a day = 1, x1 a day = 2, x2 or more a day = 3). Treatment response was evaluated by pain relief, categorised as complete (CR), at least 50% (PR) or < 50% (NR). Also, time to pain relief Response duration (RD); survival (OS); pain-free survival (PFS) Quality of life (QOL) was measured by % net relief (%NPR), obtained by dividing PFS by OS x 100. QOL was also assessed by comparing performance scores, pain and narcotic scores before and after treatment. Toxicity analysis (only available for 75% of patients).
Follow up: Pain and narcotic evaluations were mandatory before randomisation and were repeated 'at various intervals of time' afterwards.
Results: Pain relief: 91% patients overall responded to therapy: CR schedule A = 63% CR schedule B = 43% CR schedule C = 32%

Between A and B, $P = 0.016$ but nsd between A and C (presumably because of variation in data but no confidence intervals were reported).

Time to pain relief:

Schedule A = 6 days

Schedule B = 9 days

Schedule C = 8 days (nsd between groups)

Median survival time:

Schedule A = 175 days

Schedule B = 104 days ($P = 0.042$ compared to A and C)

Schedule C = 155 days

For breast primaries = 177 days

OS (for breast primaries = 198-214 days overall):

Schedule A = 206 days

Schedule B = 146 days ($P = 0.023$ compared to A and C)

Schedule C = 171 days

For breast primaries = 203 days

PFS (for breast primaries = 134-153 days overall):

Schedule A = 155 days

Schedule B = 101 days ($P = 0.034$ compared to A and C)

Schedule C = 112 days

For breast primaries = 144 days

QOL:

Mean %NPR overall = 71%

Schedule A = 72%

Schedule B = 65%

Schedule C = 75% (nsd)

For breast primaries = 70%

Using other forms of evaluating QOL, there is a trend towards improvement after HBI but no statistics are presented. The bar chart does not show marks of significance (e.g. stars or P-values) on the data.

Toxicity:

Grade 3 or 4 toxicity = 18 patients overall (12%) and nsd between treatment arms but there was significance between the two main HBI fields:

UHBI: upper GI tract (nausea & vomiting)

Schedule A = 13%

Schedule B = 23%

Schedule C = 11%

LBI: lower GI tract (diarrhoea & discomfort)

Schedule A = 4%

Schedule B = 11%

Schedule C = 12%

General comments:

This paper presented a multi-national (6 countries) RCT of three regimes of hemi-body irradiation (HBI) for the pain palliation of bone metastases due to various cancers including breast cancer ($n = 72$). Patients were recruited between March 1996 and January 1999.

For the first year, randomisation was done from a central point but, due to certain technical difficulties, was later carried out at individual participating centres. Data was collated and analysed at a central point.

Patients were stratified by ECOG performance score and by type of hemi-body irradiation field (upper, middle or lower) to be treated. Analysis showed that there were no significant differences in survival between these sub-groups.

All patients had multiple symptomatic bone metastases and 8% also had visceral metastases (not known if MBC). 91% had ≥ 15 lesions. Although technically this appears to be a thoroughly conducted study, there is a high likelihood of bias in data reporting due to several factors - there were no details of randomisation or allocation (blinding may have been unachievable given the nature of the treatment protocol). Efficacy and survival data appear to have been analysed statistically (since P values have been given for most comparisons) but there were no confidence intervals reported, just point estimates. This means that external validity is absent - data could not safely be compared with those from other studies and is only partly relevant to MBC patients anyway.

The authors concluded that schedule B, which delivers the highest daily dose in the shortest time frame results in a higher level of acute toxicity, a poorer quality of life, pain relief, MST and OS. Schedule C appears to be as effective as schedule A and might be suitable for developing countries constrained by a shortage of time and money.

Wardley <i>et al.</i> (2005)
Design: Randomized controlled trial (prognosis), evidence level: 1- Country: United Kingdom
Inclusion criteria: Histologically confirmed BC At least 1 bone metastasis confirmed by radiography Receiving hormone therapy for BC ECOG 0-2 Written informed consent
Exclusion criteria: Current chemotherapy Abnormal renal function
Population: Number of patients = 101, age range 37 to 87 years, mean age = 60 years.
Interventions: Zoledronate at 4mg via 15 min i.v. infusion every 3 weeks for up to 9 months. Patients received a stabilising treatment in hospital of up to 3 cycles and were then randomised to continue treatment at home or at hospital. After 3 cycles in this setting, patients were crossed over to the other arm and received a further 3 cycles. Group A: hospital then community (n = 45) Group B: community then hospital (n = 56).
Outcomes: Primary: efficacy by evaluation of bone pain (BPI), quality of life (QOL by EORTC QLQ-30), performance status and patient satisfaction. Secondary: safety and tolerability, assessed by monitoring of renal function and recording adverse events.
Follow up: BPI and EORTC evaluations were performed at baseline, at the end of each treatment cycle and

the final visit.

17 patients did not complete the full course of treatment, 12 in group B and 5 in group A.

During the study period, 7 patients died of disease progression and 1 from a non-treatment and non-disease related cardiac event.

Results:

Efficacy was evaluated on the intention to treat population i.e. patients who had received at least one dose of zoledronate, provided baseline data and at least one post-treatment evaluation.

Baseline scores for both groups appeared to be similar but there was no formal testing of homogeneity.

127 patients were initially screened and started the first phase of stabilisation but 26 were unable to be randomised because of disease progression.

Safety:

Renal function was normal for all patients throughout the study although mean serum creatinine values were higher in patients during their treatment in the community setting in both groups. This may have been due to the method of analysis.

Adverse events were mild and included flu-like symptoms, nausea, arthralgia, headache, pain and vomiting. Grade 3 events were experienced by 32 patients but these are not separately reported. Only 2 such events were related to medication and none resulted in treatment discontinuation.

Efficacy:

Pain reduction in comparison with baseline for the entire population:

Worst pain in past 7 days: P = 0.008

Average pain in last 7 days: P = 0.039

Interference with general activity: P = 0.012

Interference with walking ability: P < 0.001

Interference with normal work: P = 0.005

Interference with enjoyment of life: P = 0.005

Interference with sleep: P = 0.015

However, the BPI composite score was not significantly different from baseline (mean score = -0.5 P = 0.077)

Pain reduction for patients in the community setting was greater than the hospital crossover setting as follows:

Worst pain in past 7 days: P = 0.021

Average pain in last 7 days: P = 0.003

Pain right now: P = 0.013

Interference with general activity: P < 0.001

Interference with mood: P = 0.036

Interference with walking ability: P < 0.001

BPI composite score: P = 0.008

Compared with baseline, interference with work improved significantly in both the community (P = 0.011) and hospital settings (P = 0.015).

Quality of life (EORTC QLQ-C30):

There was a significant increase in mean scores for overall global health status compared with baseline (P = 0.013). There were also significant increases in mean scores for physical functioning (6% P = 0.03), emotional functioning (8% P = 0.005), and social functioning (7% P =

0.043) compared with baseline.

Zoledronate in the community setting resulted in a significant improvement in physical functioning (P = 0.018), role functioning (P = 0.001) and social functioning (P = 0.026) compared with the hospital setting.

Other improvements of community compared with hospital treatment included patient assessed improvement in pain and diarrhoea scores (P = 0.031), pain scores (P = 0.022), financial difficulties P = 0.004).

For the breast module (BR23), patients reported significant declines in future perspective with a median decrease of 17% (P < 0.0001) in the entire population, compare with baseline. Sexual function significantly increased in the community setting with a mean increase of 4% (P = 0.049) but arm symptoms were worse in the community setting and improved by 3% in the hospital setting (P = 0.004).

There were no significant changes in ECOG performance status in patients compared with baseline.

Overall, patients were satisfied with the zoledronate treatment but more so in the community setting.

General comments:

This paper detailed a randomised phase, open label crossover trial which compares safety and efficacy of treatment with zoledronate at home and in the hospital.

Raw scores for QOL questionnaire were converted to derived scores and then analysed using a mixed effect model (period and treatment were fixed effect and subject was the random effect).

There are no details of randomisation.

The patients in this study are a specific group, defined by the stage of their disease (early by virtue of hormone treatment rather than chemotherapy) and therefore the findings are not necessarily applicable for MBC patients as a whole.

Overall, there was an improvement in pain and well being without adverse effects in favour of treatment in the community. There may also be indications for cost effectiveness.

Weinfurt *et al.* (2004)

Design: Prospective cohort study (prognosis), evidence level: 2-
Country: United States

Inclusion criteria:

Histologically confirmed BC
At least 1 bone metastasis confirmed by radiography
Ambulatory
Over 18 years
ECOG status 0-3
In receipt of anti-neoplastic therapy
Good clinical condition
Not more than 2nd line endocrine therapy unless combined with chemotherapy

Exclusion criteria:

Pregnancy
Treatment with bisphosphonates < 12 months before 1st visit

<p>Lymphangitic lung metastases Symptomatic brain metastases History of treatment non-compliance or unreliable behaviour Grade III or i.v. heart disease</p>
<p>Population: Number of patients = 1124, mean age = 58 years.</p>
<p>Interventions: Zoledronate at 4 mg (n = 377) or 8 mg (n = 360) as a 5 min i.v. infusion or pamidronate at 90 mg (n = 387) by 90 min i.v. infusion every 3-4 weeks for 12 months in addition to current anti-cancer treatment.</p> <p>At some unspecified point, patients were removed from the 8 mg zoledronate dose and were put on 4mg as a 15 min i.v. infusion (8/4 mg).</p>
<p>Outcomes: Health related quality of life.</p>
<p>Follow up: Baseline data collected included age, education, employment status, geographic region, current therapy, treatment group, previous SRE, days from initial cancer diagnosis to randomisation and days from first bone metastasis to randomisation.</p> <p>Quality of life (QOL) was assessed by analysis of FATG questionnaires completed by patients at baseline and after 12, 24, 36 and 51 weeks on arrival at the clinic and before seeing the physician or receiving medication. Data were analysed on the intention to treat principle.</p> <p>The percentage of patients completing the full course of treatment was 63% in the 4mg zoledronate arms and 60% in each of the other two arms. 30% of the drop-outs were due to adverse events and 26% to death.</p>
<p>Results: The Authors concluded that over a 1 year period, the average patient on these treatments experienced a gradual improvement in overall, physical, functional and emotional wellbeing.</p> <p>The results were illustrated by non-linear, 2nd or 3rd degree polynomial growth curves for FATG data: emotional and functional well-being - the lack of linearity was due to an initial increase followed by a plateau effect. These models did not fit data for the social/family well-being which was therefore uninterpretable.</p> <p>There were significant variations among women in their experiences over time some of which were explained by differences in baseline status due to factors discussed above.</p> <p>Women who had previously experienced a SRE before starting treatment began the study with significantly worse physical and functional well being. Authors conclude by saying that the positive mean change in health related QOL observed for patients treated with either regime was consistent with the notion that prevention of SREs could lead to a better QOL.</p>
<p>General comments: This paper details a double blind, randomised controlled trial of two doses of zoledronate against pamidronate in patients with either multiple myeloma or stage i.v. breast cancer. The results for quality of life are reported here for only the latter group.</p> <p>The trial was conducted at 207 centres in Canada, the USA, South America, Europe, Australia, New Zealand, Scandinavia and South Africa.</p>

Health related QOL scores were analysed by conditional and unconditional models that took into account covariates that might explain variations between patients. These models appear to be complex but are thoroughly described. The covariates are as described by demographic data collected from each patient at baseline e.g. age, education etc. ECOG status was dichotomised and incorporated into the model.

This paper was predominantly based on testing the models to predict outcomes and contains little useful information on the treatment per se.

Pecherstorfer <i>et al.</i> (2006)
Design: Prospective comparative study (harm), evidence level: 2- Country: Austria
Inclusion criteria: Histologically confirmed breast cancer with radiologically confirmed bone metastases WHO performance status of 0-2 Minimum age = 18yrs Written informed consent
Exclusion criteria: Pregnant or breast feeding Serum creatinine > 3 mg per dl Paget's disease of the bone Primary hyperparathyroidism History of aspirin sensitive asthma Aminoglycoside antibacterial within 4 weeks
Population: Number of patients = 62, age range 36 to 75 years, mean age = 55 years.
Interventions: 6mg ibandronate i.v. over 1-2hrs every 3/4 weeks for a maximum of 96 weeks
Outcomes: Primary outcome: long term safety and tolerability as assessed by adverse events and laboratory evaluations
Follow up: Laboratory measures were made every 4 weeks up to week 12 and then every 12 weeks. 9 patients died in this extension phase but none were ascribed to treatment
Results: Of the 62 patients receiving treatment, 16 had previously received placebo (P/6 mg) and 46 patients had previously received 6mg ibandronate (6/6 mg). Adverse events were experienced by: P/6mg: 100% patients when in the RCT then 68.8% in the extension 6/6mg: 95.7% patients when in the RCT then 80.4% in the extension Treatment-related events (including headache, bone disorder, joint disorder, muscle cramps, chills, gastroenteritis, breast pain, rash and dyspnoea): P/6mg: 56.3% in the RCT then 6.3% in the extension 6/6mg: 67.4% in the RCT then 13.0% in the extension Serious adverse events (predominantly progression due to malignancy):

P/6mg: 31.3% in the RCT then 18.8% in the extension
6/6mg: 26.1% in the RCT then 28.3% in the extension

Adverse events leading to withdrawal (including leg thrombosis, arrhythmia):
P/6mg: 12.5% in the extension
6/6mg: 8.7% in the extension

Adverse events leading to death:
P/6mg: 6.3% in the extension
6/6mg: 11.4% in the extension

Median treatment duration for P/6 mg was 28.5 months (range:20-40) and for 6/6 mg was 29.5 months (range: 21-41).

Changes in serum creatinine from baseline to study end were not significantly different between groups.

General comments:

This paper describes a post-trial (MF4265) study that offered patients previously randomised to three/four weekly 2 mg i.v. bolus (n = 154) or 6 mg i.v. ibandronate (n = 154) or placebo (n = 158), a continuation of ibandronate for a further 96 weeks. The purpose was to study long term safety.

Original randomisation was by pre-determined randomisation list (presumably block) and the study had been blinded with respect to placebo or ibandronate (but open label with regard to ibandronate dose due to mode of delivery). Since in this trial the 6 mg dose of ibandronate was superior in efficacy to placebo or a lower dose (2 mg) this dose was chosen for further reporting.

Safety outcomes are reported for all patients who received at least one post-study dose of ibandronate and had at least one follow-up assessment.

Low patient numbers overall and inequality of group size complicates interpretation but the authors claim long term safety of i.v. ibandronate particularly with regard to renal function. However, all the data are presented as percentages (no confidence intervals) and there are no statistical analyses of the raw data to show whether or not the recorded differences between the outcomes for the two arms were significant.

Sciuto *et al.* (2001)

Design: Prospective comparative study (therapy), evidence level: 3

Country: Italy

Inclusion criteria:

Breast cancer

Pain arising from bone metastases resistant to chronic analgesia (opiates or NSAIDs)

Progressive bone disease as measured by technetium uptake in multiple foci

Platelets > 100,000 per mm³

Leucocytes > 4,000 per mm³

Serum creatinine <0.15 mmol per l

Life expectancy > 3 months

Written informed consent

Exclusion criteria:

None stated

<p>Population: Number of patients = 50, age range 22 to 70 years.</p>
<p>Interventions: Group A: Single i.v. bolus of Sr-89 at 148 MBq (n = 25) Group B: Single i.v. bolus of rhenium-186 hydroxyethylidene diphosphonate (Re-186-HEDP) at 1406 MBq (n = 25)</p>
<p>Outcomes: Primary outcome: pain palliation based on pain score improvement determined by the patient. The test statistic was based on the division of patient responses into the equivalent of complete response (CR), partial response (PR) and minimal response (MR). Time to response and duration of response were also measured.</p> <p>Pain was rated on a modified Wisconsin test with 5 scores: 0 = no pain + normal sleep + no analgesia</p> <p>1 = occasional pain + occasional waking + occasional analgesia (no narcotics aspirin or NSAIDs).</p> <p>2 = mild continuous pain + usual waking + usual analgesia (no narcotics e.g. aspirin or NSAIDs)</p> <p>3 = moderate continuous pain + waking + usual analgesia including narcotics or not (e.g. codeine)</p> <p>4 = severe continuous pain + no sleep + resistant to strong narcotics (e.g. morphine)</p> <p>Secondary outcomes: Karnofsky performance scale (KPS) improvement and bone disease progression.</p>
<p>Follow up: All patients received baseline bone scintigraphy, evaluation of haematological and renal function plus conventional imaging and scans.</p> <p>Symptoms were also evaluated to confirm that pain was due to bone metastases rather than some other cause. Pain was assessed at baseline according to the modified Wisconsin test.</p>
<p>Results: Mean Wisconsin test score for group A = 1.0 ± 0.8 post-treatment compared with baseline score of 2.6 ± 1.1 ($P < 0.05$) Mean Wisconsin test score for group B = 1.0 ± 1.0 post-treatment compared with baseline score of 2.9 ± 0.7 ($P < 0.05$)</p> <p>Mean KPS score for group A = 79 ± 23 post-treatment compared with a baseline score of 61 ± 18 ($P < 0.05$) Mean KPS score for group B = 78 ± 16 post-treatment compared with a baseline score of 61 ± 20 ($P < 0.05$)</p> <p>Mean bone scintigraphy score for group A = 2.3 ± 0.8 post-treatment compared with a baseline score of 2.4 ± 0.7 Mean bone scintigraphy score for group B = 2.9 ± 0.9 post-treatment compared with a baseline score of 2.9 ± 0.9</p> <p>Overall pain relief (CR+PR+MR) group A = 84% (95%CI: 65-94) Overall pain relief (CR+PR+MR) group B = 92% (95%CI: 55-99) ($P = 0.66$) Median time to pain relief group A = 21 days Median time to pain relief group B = 4 days</p>

<p>Mean duration of pain relief group A = 125 days (med 120 days) Mean duration of pain relief group B = 107 days (med 60 days)</p> <p>Duration of response was positively correlated with degree of the response ($P < 0.05$) and KPS ($P < 0.05$) in both groups.</p> <p>Adverse events: mild flare-up of pain was experienced by 30% of patients overall. Group A patients had grade 1 ($n = 1$) or grade 2 ($n = 2$) haematological toxicity. Group B patients also had grade 1 haematological toxicity ($n = 3$).</p>
<p>General comments: This paper describes a small comparative study of two radiopharmaceuticals, rhenium and strontium with 25 patients in each group. The trial was open label.</p> <p>Although authors stated that patients were randomised there are no details of how this was practically achieved. This leads to an obvious possibility of bias.</p> <p>Patient characteristics are not given per group but KPS, Wisconsin and bone scintigraphy scores appear to be similar at baseline.</p> <p>Authors state that there was no significant difference between groups in respect of global response or duration but onset of response was significantly quicker in group B ($P < 0.0001$). There was also no significant difference in KPS score improvement between groups.</p> <p>The lack of information about patient characteristics and methods of randomisation make this of evidentially lower value.</p>

<p>Baziotis <i>et al.</i> (1998)</p>
<p>Design: Prospective case series (therapy), evidence level: 3 Country: Greece</p>
<p>Inclusion criteria: Metastatic breast cancer Suffering extreme pain (10 on pain scale - see below) Multiple (≥ 5) bone metastases WBC $\geq 3,000$ per mm^3 Platelets $\geq 100,000$ per mm^3 Ht $> 30\%$ Hb > 10 g per dl</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 64.</p>
<p>Interventions: Single i.v. injection of Sr-89 at a dose of 150 MBq (4 mCi)</p> <p>10 patients received a second, and 5 a third, dose but the outcomes reported in this document only relate to the first treatment.</p>
<p>Outcomes: Pain reduction as measured on a scale of 0 (no pain)-10 (most severe) scale compared with an baseline score of 10.</p>

<p>Patients moved from 10 to the following: (2.5-0) - dramatic response: sleep all night without analgesia (5-2.5) - satisfactory response: sleep all night with analgesia (7.5-5) - moderate response: sleep half night (10-7.5) - no response: no sleep at all</p>
<p>Follow up: Baseline laboratory tests were repeated every week for 8 weeks. Pain intensity was evaluated before treatment and every 10 days thereafter.</p> <p>Bone scintigraphy (99 mTcMDP) images were obtained at baseline and 3 months after treatment. Sr-89 bremsstrahlung images were obtained to show localization to tumour sites.</p> <p>Follow-up period was 6 months.</p>
<p>Results: 81% patients experienced pain palliation with reduction in analgesia requirement. These 52 patients reported:</p> <p>Dramatic response (35%) Satisfactory response (40%) Moderate response (25%)</p> <p>These improvements were generally recorded between 10-20 days after the injection.</p> <p>78% patients had a decrease in peripheral blood cell counts which returned to pre-treatment levels after 4-6 weeks with full recovery in the following 3-5 weeks but 5 patients required colony-stimulating factor.</p> <p>Most (not quantified) patients showed no improvement in bone scintigraphy. 3 patients showed improvement.</p>
<p>General comments: This paper describes a small prospective case series of 64 MBC patients who received a single dose of Sr-89 for pain palliation.</p> <p>Analgesia was standardised for all patients throughout the study.</p> <p>Follow-up was sufficiently long to measure the outcome and included all patients.</p> <p>The study is very weak evidence as there is no control, such as an analgesic or placebo, with which to compare the effects of strontium.</p>

<p>Berna <i>et al.</i> (1995)</p>
<p>Design: Prospective case series (therapy), evidence level: 3 Country: Spain</p>
<p>Inclusion criteria: Breast cancer with skeletal metastases refractory to opioid analgesia and/or RT WBC $\geq 3,500$ per mm^3 Platelets $\geq 100,000$ per mm^3</p>
<p>Exclusion criteria: None stated</p>
<p>Population:</p>

Number of patients = 15, age range 47 to 83 years, mean age = 61 years.
Interventions: Single i.v. injection of Sr-89 at doses between 118-148 MBq
Outcomes: Primary outcome: pain relief. Pain severity was scored from a combination of clinical status, mobility, sleeping pattern, number of painful sites, pain intensity and analgesia requirement.
Follow up: Baseline evaluations of clinical status, sleeping pattern, pain severity and analgesia dependency were repeated at 4, 8 and 12 weeks after treatment.
Results: Overall pain relief and reduction of analgesia = 47% Substantial improvement with reduction of pain > 50% (range: 55-71) = 20% Mild to moderate improvement with reduction of pain severity < 50% (range: 34-47) = 27% No response = 53% Response duration ranged from 3-7 months Decreased peripheral blood cell count = 73%
General comments: This is a very small case series of patients receiving Sr-89 for pain palliation. All had multiple bone metastases diagnosed between 2 and 10 years previously. Authors point out that all patients continued to take analgesics throughout the follow-up period which confounds the assessment of efficacy of the treatment alone. This observational study offers only a very weak level evidence in favour of the strontium-89 for pain palliation.

Kasalicky & Krajska (1998)
Design: Prospective case series (therapy), evidence level: 3 Country: Czech Republic (sometimes also rendered as Czechia)
Inclusion criteria: Skeletal metastases WBC ≥ 2,500 per mm ³ Platelets ≥ 100,000 per mm ³ Life expectancy > 3 months
Exclusion criteria: None stated
Population: Number of patients = 23.
Interventions: 118 patients received a single i.v. injection of Sr-89 at a dose of 150 MBq Overall, 76 patients received a second, 36 a third, 21 a fourth and 8 a fifth dose. Total doses = 256 (number not stated for MBC patients).

A second dose was given not less than 3 months after the initial treatment. Only initial treatment results are presented by sub-group.

Outcomes:

The sum of several factors:

Change in condition: subjective by patient (-1 to +2)

Analgesia: objective by medical staff and by patient (-1 to +3)

Mobility: subjective - pain sensation when walking (-1 to +2)

Pain palliation: subjective by patient & analgesia use (-1 to +2)

Follow up:

Baseline Karnofsky performance scale (KPS) was assessed together with routine examination including biochemical and haematological criteria, ECG and routine X-rays. Frequency of follow-up assessment was not stated.

Skeletal disease was confirmed by scintigraphy (99 mTcMDP).

Follow-up period was 3 years during which time 76 patients (64.4% of study total) died.

Results:

Scores after first treatment

Change in condition:

Mild improvement = 10

Definite improvement = 13

Analgesics:

Quantity decreased by 20-45% = 15

Quantity decreased by 50-80% = 7

Analgesics discontinued = 1

Mobility:

Unchanged = 2

Less restricted = 20

Unrestricted = 1

Pain palliation:

Unchanged = 2

Mild pain relief = 3

Marked relief or no pain = 18

Overall score after first administration:

Mild improvement = 10 (43.5%)

Substantial improvement = 10 (43.5%)

Dramatic improvement = 3 (13%)

Mean duration of benefit (number of patients not known):

1st dose = 3.08 months (\pm 0.48)

2nd dose = 3.58 months (\pm 0.92)

3rd dose = 3.88 months (\pm 1.21)

4th dose = 5.63 months (\pm 3.0)

5th dose = 5.33 months (\pm 2.36)

General comments:

This paper reports a larger prospective case series which enrolled patients with various primary cancers, including 23 with MBC. Only the response to first dose was given in sub-groups.

This works suffers the usual shortcomings of an observational study without a control and the patient number is very low.

Pons *et al.* (1997)

Design: Prospective case series (therapy), evidence level: 3
Country: Spain

Inclusion criteria:
MBC with multiple (not defined) bone metastases
Bone pain
Bad response to conventional analgesia
Platelets > 100,000 per mm³
Leucocytes > 3,000 per mm³
Life expectancy > 3 months

Exclusion criteria:
-

Population:
Number of patients = 26, age range 39 to 70 years, mean age = 58 years.

Interventions:
Single i.v. injection of Sr-89 at a dose of 148 MBq (4mCi)

16 patients received a second, and 3 patients a third, dose at a point when, following a previous treatment, measurable pain returned.

Outcomes:
Efficacy of pain palliation as measured by assessment of pain score, analgesia score and KPS:

Good response: increase in KPS, decrease in pain (≥ 4) and analgesia (≥ 1) scores
Partial response: increase in KPS, decrease in pain (2 or 3 points) and no change in analgesia scores
No response: No variation or decrease in KPS, no variations or an increase in pain or analgesia scores

Follow up:
Baseline physical examination, Karnofsky performance assessment, blood count, laboratory testing and bone scintigraphy was performed. Full blood counts were re-assessed at 1, 3 and 6 months after treatment.

Pain score was calculated as the product of severity (0-3) and frequency (0-3). Analgesia score was assessed on a 5-point scale (EORTC). Pain relief was assessed 3 months after each treatment.

The extent of skeletal involvement was calculated by bone scan index (BSI) from 0-100 (Blake). Scans were evaluated by independent reviewers.

Follow-up was for a period of 6 months. 5 patients died before this time and hence their clinical response was not evaluated.

Results:
Pain decreased during the 2nd or 3rd week after treatment and reached a peak in weeks 5 and 6.

Clinical response (n = 26 doses)

<p>Good: 62% (35% of which involved both a decrease in pain and analgesia and 27% of which were incomplete) Partial: 31% No response: 8%</p> <p>No patients required blood transfusion for haematological depression. Whilst platelets and leucocytes were depressed, they returned to normal values within 6 months. Grade 1 or 2 leucocyte toxicity occurred in 19% MBC patients and grade 1 thrombocytopenia was also experienced by 19% of this group.</p>
<p>General comments: This paper reports a prospective case series of 76 patients of who only 26 had MBC but whose outcomes were reported separately. All patients received Sr-89 for pain palliation; some in multiple doses over time.</p> <p>This paper deals with a mixed population of prostate and MBC patients and only the first treatment outcome was reported by sub-group.</p> <p>Of 16 patients receiving subsequent doses of Sr-89, 4 had MBC but efficacy was reported overall - the clinical response to the second dose was good (63%) and partial (37%).</p> <p>Incomplete responses were scored as 'good' which obviously could give an over inflated assessment of efficacy.</p> <p>The authors reported no decrease in tumour markers and therefore opine that SR-89 is not tumoricidal.</p>

Borojevic <i>et al.</i> (1999)
<p>Design: Prospective case series (prognosis), evidence level: 3- Country: Serbia and Montenegro</p>
<p>Inclusion criteria: Histologically proven breast cancer Osteolytic metastases verified radiographically Bone only metastases</p>
<p>Exclusion criteria: None reported</p>
<p>Population: Number of patients = 386, age range 27 to 77 years, median age = 52 years.</p>
<p>Interventions: Short RT regimes (n = 122): 14 Gy in 2 fractions with 48hr interval 16 Gy in 4 fractions in 4 days</p> <p>Medium RT regimes (n = 250): 18 Gy in 6 fractions in 6 days 20 Gy in 8 fractions in 8 days</p> <p>Long RT regimes (n = 14): 30 Gy in 10 fractions in 14 days 40 Gy in 20 fractions in 28 days</p>
<p>Outcomes:</p>

<p>Efficacy, possible impact on quality of life (QOL) and overall survival (OS).</p> <p>Efficacy was measured using a numerical radiobiological (time/dose/fractionation) factor TDFf - no further description.</p> <p>Follow-up assessment of metastases was graded according to UICC criteria: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).</p>
<p>Follow up: Assessment of the effect of treatment was carried out after 2 and 4 months. There are no details of baseline testing.</p>
<p>Results: The TDFf was similar for the low and medium RT regimes (range: 36.8-38.9) whilst the TDFf was 61.6 for the 30 Gy long RT regime and 66.1 for the 40 Gy regime.</p> <p>There were significant improvements in lesion response between the 1st and 2nd assessments in patients receiving short and medium RT regimes: 14 Gy (P = 0.004), 16 Gy (P = 0.0001), 18 Gy (P = 7.77 x 10E-5) and 20 Gy (P = 1.11 x 10E-9).</p> <p>The overall response rate was 29% (n = 112) at the first evaluation but, at this point responders and non-responders were not significantly different in terms of their survival (P > 0.05). By the second assessment point, however, those patients with favourable radiographic findings had superior survival to those patients who did not (P < 0.01).</p> <p>Median OS = 31 months (range: 4-310).</p> <p>Median OS for patients with bone-only metastases is not reported but, from the Kaplan Meier graph appears to be in excess of 60 months. 2yr survival is 97.6%, 3 yr survival is 67.36% and 5 yr survival is 45%. Some of these patients developed visceral metastases later in the study and had a shorter survival time (P = 0.01).</p>
<p>General comments: This is a prospective non-randomised trial undertaken between 1988 and 1996 in former Yugoslavia. Patients were allocated to one of 6 different RT fractionation regimes for either solitary (n = 68) or multiple (n = 318) bone metastases from breast cancer.</p> <p>Some of the patients have solitary bone metastases and some patients had bone metastases as part of wider metastatic disease but the data are not separately reported for these groups.</p> <p>This paper pre-dates the systematic review on RT fractionation, and is poorly reported (in some cases contradictory). One outcome (QOL) is not reported at all.</p>
<p>Gerszten <i>et al.</i> (2005)</p>
<p>Design: Prospective case series (prognosis), evidence level: 3- Country: United States</p>
<p>Inclusion criteria: -</p>
<p>Exclusion criteria: -</p>
<p>Population: Number of patients = 50, age range 36 to 77 years, mean age = 56 years.</p>
<p>Interventions: Cyber Knife Image-Guided Radiosurgery System with Dynamic Tracking System software.</p>

<p>Patients received a tumour dose of 12.5-22.5 Gy (mean 19) depending on location:</p> <p>Cervical and thoracic spine: 19 Gy (range: 15-22.5) Lumbar spine and sacrum: 20 Gy (range: 15-22.5)</p>
<p>Outcomes: Pain relief was evaluated on a 10-point visual analogue scale with intensity description, where 0 = no pain and 10 = worst imaginable pain.</p>
<p>Follow up: Median follow-up = 16 months (range: 6-48). Baseline pain assessment was repeated 1 month after radiosurgery.</p>
<p>Results: 32 patients had a solitary metastasis and 18 had multiple bone metastases: 68 lesions were treated. There were no clinically detectable radiological signs attributed to radiation-induced acute or sub-acute spinal cord damage. Nor were these apparent from post-treatment MRI scans. No patient experienced exacerbation of symptoms, haemorrhage or neurological deficit after treatment and no patient developed radiation-induced myelopathy or radiculopathy during follow-up. Pain relief: 96% of patients reported a long term improvement in pain in comparison with baseline values. The improvement was rated from 0 (n = 2) for patients that received no benefit to 9 for patients that experienced complete resolution of pain (mean absolute improvement = 5).</p>
<p>General comments: This paper presents a small case series of patients treated with radiosurgery for spinal breast metastases either as primary therapy, for tumour progression, as a boost after surgery or for progressive neurological defect. The predominant outcome was alleviation of pain. 48/50 patients had received previous RT to the area and were therefore unable to receive further conventional RT. There is very little in the way of evidential value in this paper which is largely composed of illustrative case histories and how they were approached. There were no statistics.</p>

<p>Durr <i>et al.</i> (2002)</p>
<p>Design: Retrospective case series (prognosis), evidence level: 3 Country: Germany</p>
<p>Inclusion criteria: None stated</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 70, age range 31 to 83 years, mean age = 57 years.</p>
<p>Interventions: Surgery:</p>

Incisional biopsy = 4
Resection of proximal humerus without reconstruction = 1
Dorsal decompression = 11
Dorsal decompression with additional instrumentation = 15
Partial vertebral resection = 3
Tumour resection and implantation of endoprosthesis = 15
Standard hip arthroplasty = 7
Knee endoprosthesis = 1
Intralesional resection with cementation and instrumentation = 12
Acetabular resection and reconstruction = 1

6 patients with a solitary metastasis had wide tumour resection whilst 60 patients had a palliative intralesional or marginal procedure or, in the remaining 4 patients, a biopsy.

Outcomes:

Survival

Follow up:

The 12 patients alive at the end of the study were followed for a mean of 41.6 months (range: 2-131) median = 34.5 months.

Results:

The most common locations of metastases were in the spine (n = 29) and proximal femur (n = 27) with other lesions in the humerus, femoral shaft and pelvis. 17 patients had spinal fractures and 22 had fractures in the extremities (including 15 in the proximal femur). 10 patients had neurological impairment due to spinal cord compression, 6 had thoracic involvement and 4 with lumbar compression.

19 patients had a solitary metastasis, 19 had multiple bone lesions and 32 patients had other visceral involvement.

58 patients had died from their disease by the end of the study. 6 died within 30 days of surgery.

14 patients had post-surgical complications including pulmonary dysfunction (n = 4), cardiac insufficiency (n = 3), neurological impairment (n = 2), post-operative bleeding (n = 2), multi-organ failure (n = 1), deep infection (n = 1), thromboembolus (n = 1), pseudoarthrosis (n = 1) and failure of osteosynthesis (n = 2). Only 3 of these patients had received pre-surgical treatment with RT or chemotherapy.

No patients had local tumour recurrence or progression.

12/19 patients with a solitary metastasis died because of progressive disease; 3 had progressive at the time of publication and 4 were free of tumour (3 of them for > 5 yrs). 5yr survival rate is therefore 39%.

17/19 patients with multiple metastases without visceral involvement died because of progressive disease; 2 patients were alive at the time of publication.

29/32 patients with multiple metastases as part of widespread disease died. 3 patients were alive at the time of publication, all with disease and less than 12 months follow-up.

Overall, the survival rate at 1 year was 59%, after 2 years 36%, after 5 years 13% and 7% after 10 yrs. The most predictive factors for survival were involvement of multiple bone and visceral spread. Patient age and time from diagnosis to surgery were not significantly associated with survival.

Patients receiving chemotherapy before surgery had a significantly worse prognosis than those receiving chemotherapy after surgery.

General comments:

This paper details the experiences of a German centre in its surgical treatment of women with bone metastases due to breast cancer between 1980 and 1998.

This is an observational study without comparators and thus has the usual limitations. Whilst appropriate analysis has been performed i.e. Kaplan Meier survival analysis, Cox regression, survival data are poorly presented i.e. without confidence intervals.

Coronado *et al.* (2006)

Design: Retrospective case series (therapy), evidence level: 3-
Country: Spain

Inclusion criteria:
Written informed consent

Exclusion criteria:
None stated.

Population:
Number of patients = 64, age range 33 to 100 years, median age = 66 years.

Interventions:
Mean dose of 2479 MBq Samarium was administered as a single treatment.

Some patients received more than 1 treatment with a mean dose of 4694 MBq. The mean interval between successive treatments was 7.5 months (range: 3-12)

Outcomes:
Pain: recorded by patients on a visual analogue scale (VAS) from 0 (no pain)-10 (worst imaginable pain).

Analgesia: need was assessed according to the WHO analgesia scale.

ECOG status.

Clinical benefit was graded:

Complete response: VAS of 0 and/or no analgesia

Moderate response: > 2 VAS decrease, any decrease in analgesia and/or ECOG status

Minor response: ≤ 2 VAS decrease and the same analgesia and/or ECOG status

No response: Stabilisation or worsening of pain, analgesia need or ECOG status.

Follow up:

Baseline data were collected on pain intensity, analgesia needs and performance status. These assessments were repeated 4 weeks after treatment. Patients that had received two treatments were evaluated twice.

Haematological toxicity and renal function were also assessed at baseline and after treatment.

Two people appear to have not been assessed for clinical benefit - the reasons for this are not given.

Results:

28/64 patients (44%) had MBC and 36% had metastases other than to bone. 62/64 patients were evaluable.

Pain relief:

<p>51/26 (82%) patients reported pain relief</p> <p>21/62 patients completed both 'before' and 'after' VAS questionnaires and in this group there was a significant decrease in pain intensity after treatment - the median VAS decreased from 8 to 3 (P < 0.001)</p> <p>Analgesia consumption: 29/62 (55%) reduced analgesia consumption. 23/62 (37%) remained stable and 1 patient increased analgesia. The decrease in analgesia consumption was significant (P < 0.001)</p> <p>ECOG status: 22/62 (43%) patients improved their ECOG status after treatment (P < 0.001)</p> <p>Clinical benefit: 53/62 (85%) derived a clinical benefit from samarium treatment. 6 patients with breast cancer showed a complete response.</p> <p>Median time to onset of improvement was 7 days (range: 3-30) and pain relief persisted for a mean of 3 months (range: 0.5-12)</p> <p>Adverse events: One patient suffered grade 4 toxicity (leukopenia).</p>
<p>General comments: This paper present a small retrospective case series of patients treated with Sm153 for painful bone metastases between 2000 and 2004.</p> <p>This is poor quality evidence, both in terms of low patient number but also because the data are presented as point estimates. There are no comparators against which to measure these benefits.</p>

Gristina <i>et al.</i> (1983)
Design: Retrospective case series (therapy), evidence level: 3- Country: United States
Inclusion criteria: Histologically proven breast cancer metastatic to bone Ambulatory > 6 weeks life expectancy
Exclusion criteria: Neurologic loss Intractable pain due to axial lesions
Population: Number of patients = 25, age range 24 to 72 years, mean age = 58 years.
Interventions: Surgery: open reduction and internal fixation with methylmethacrylate. Antibiotics were given before, during and for one week after surgery. Two weeks after surgery, radiotherapy was given (2,000 rads) to the site and continued for 2 weeks.
Outcomes: Results were rated: Good (excellent pain relief and good functional use of the involved extremity) Fair (decreased but persistent pain with improved use of the involved extremity)

Poor (No decrease in pain and no improvement in function)
Follow up: Baseline bone, liver and spleen scans were obtained
Results: Surgery was performed on the acetabulum (n = 3), femoral neck (n = 9), peritrochanteric fractures (n = 8), femur (n = 3) and humerus (n = 8). Prophylactic fixation for impending fractures was performed on femur (n = 2), femoral neck (n = 5) and humerus (n = 1). Results for these patients were compared with a randomly selected control population of patients having MBC with bony metastases but no actual or impending fractures. Pain relief and improvement in function: Good = 23 (74%), fair = 4 (13%) and poor = 4 (13%). Of the 'poor' results, 3 patients died within 3 weeks of the operation and one was due to fixation failure. Of the 'fair' results, mobility but not pain had improved in 2 patients and lack of mobility still affected the other 2 patients. Survival: Mean OS = 19.9 months with nsd between subjects of surgery and controls. Post diagnosis survival at ~7 years was 25% in both groups. At the time of publication, 6/31 patients were alive, four of which had survived > 2 years post-operatively (and 7 and 9 months for the other 2 patients). Adverse events: 3 patients died from surgery to the hip, one from pulmonary embolus and two from progressive disease but without tumour recurrence at the site of surgery.
General comments: This is a small case series from the USA reporting on outcomes of surgery on 25 patients (31 operations) with bone metastases due to breast cancer from 1973 to 1979. Authors conclude that internal stabilisation with methylmethacrylate markedly reduces pain and normal function and mobility is prolonged. This is a very low patient number, an observational study of mainly anecdotal value having little in the way of statistical power. A comparison with the control group is questionable in relevance as there is no matching of characteristics, randomisation etc.

Broos <i>et al.</i> (1993)
Design: Retrospective case series (therapy), evidence level: 4 Country: Belgium
Inclusion criteria: Metastatic fractures or impending fractures from breast or prostate cancer
Exclusion criteria: None stated
Population: Number of patients = 65, age range 38 to 94 years, mean age = 65 years.
Interventions: Surgery: Prophylactic osteosynthesis (for impending fracture) = 6 Within 48 hrs of fracture = 40

<p>Within 7 days = 59</p> <p>Endoprosthetic surgery = 36</p> <p>Osteosynthesis = 41</p>
<p>Outcomes: None specific</p>
<p>Follow up: Not detailed</p>
<p>Results: 46 patients were able to walk again, independently or with the aid of a stick. Good pain relief was obtained for 51 patients.</p> <p>Average survival time for 20 patients surviving at the end of the study (1992) was 28 months. Other patients experienced a mean survival time of 12 months (breast cancer sub-group, 13 months). 5 patients died within 30 days of the surgery.</p> <p>2 patients suffered adverse effects: one with a DVT and the other with pulmonary embolism.</p>
<p>General comments: This short paper recounts the experience of one treatment centre in Belgium between 1980 and 1990. Surgeons operated on 77 fractures in 65 patients, including 16 patients who had multiple skeletal lesions (implying that the majority had solitary lesions). 75% were breast cancer patients.</p> <p>60/77 fractures were in the proximal end of the femur (15 intracapsular, 16 trochanteric and 29 subtrochanteric). 16 fractures were in the femoral shaft and one in the supracondylar zone.</p> <p>This evidence is of anecdotal value only. Authors conclude that aggressive surgery for such patients should be performed except when the life expectancy is less than 4 weeks patients are in a poor general condition or have complete mental deterioration.</p>

<p>Warr <i>et al.</i> (2002)</p>
<p>Design: Guideline (prognosis), evidence level: 1++ Country: Canada (federal state, Commonwealth Realm)</p>
<p>Inclusion criteria: Included studies: Women with bone metastases due to breast cancer (it was not apparent whether or not patients may have had other metastatic disease or if any had solitary bone metastasis).</p>
<p>Exclusion criteria: None stated</p>
<p>Population: -</p>
<p>Interventions: Any bisphosphonate compared with other bisphosphonate, placebo or no treatment. Different doses or routes of administration of any bisphosphonate.</p> <p>Clodronate (i.v. or oral), pamidronate (i.v. or oral), ibandronate (i.v. or oral) and i.v. zoledronate were used in the included studies.</p>
<p>Outcomes: Included studies reported on at least one of the following: survival, quality of life, adverse events,</p>

bone pain (measured by pain scales and/or analgesia use) and skeletal related events (excluding hypercalcaemia).

Follow up:

-

Results:

See Cancer Care Ontario guideline:
<http://www.cancercare.on.ca/pdf/pebc1-11f.pdf>

General comments:

This guideline was originally written in 1998 and was updated in 2002 and 2004. Three patient groups were reviewed of which only the evidence for women with MBC and bone metastases is included here.

The 2002 literature search found the following relevant articles and abstracts, which are summarized in the practice-guideline report: 2 evidence-based practice guidelines from other guideline-development groups (ASCO and SIGN), 1 Cochrane systematic review with meta-analysis, published in 2002 and 28 RCTs, only 9 of which were not included in the Cochrane review.

The 2004 search found 1 update to the ASCO guideline, 1 RCT updating an abstract included in the Cochrane review, 1 RCT updating an abstract in the original guideline and the results from a study, presented in two abstracts at the 2003 San Antonio Breast Cancer Symposium, which pooled data from three RCTs to compare i.v. and oral ibandronate with placebo.

Evidence summary:

Oral clodronate and intravenous i.v. pamidronate significantly reduced skeletal events and pain in women with breast cancer metastatic to bone.

Direct comparisons found 4 mg zoledronate equivalent to 90 mg pamidronate given i.v. every 3 to 4 weeks.

Bisphosphonates did not improve survival but did reduce skeletal events and pain in women with breast cancer metastatic to bone. There was no significant difference in adverse effects between those receiving bisphosphonates and controls.

Recommendations:

1] Women with breast cancer who have bone metastases should be offered treatment with oral clodronate, intravenous pamidronate, or intravenous zoledronate.

- An exception may be patients with a short expected survival (i.e. less than six months) who have well controlled bone pain.

- Patients who have difficulty tolerating oral medications (e.g., those with nausea/vomiting or oesophagitis) should be offered intravenous pamidronate or zoledronate.

- Intravenous zoledronate may be preferable to pamidronate when a shorter infusion time (15 minutes versus two hours, respectively) is important.

- Intravenous clodronate has not been examined for its ability to reduce morbidity from bone metastases with long-term use. When clodronate is used for this purpose, the oral route is recommended.

2] In patients with bone metastases and pain, treatment with pamidronate, zoledronate, or clodronate may be a useful adjunct to conventional measures for pain control.

This guideline was appraised using the AGREE tool and found to be of high standard.

Scarantino *et al.* (1996)

<p>Design: Phase II study (prognosis), evidence level: 3 Country: United States</p>
<p>Inclusion criteria: Single or multiple bone metastases secondary to prostate or breast cancer Painful sites (1-2) confined to one hemi body field (upper, middle or lower) Pain score of ≥ 2 and narcotic score of ≥ 2 according to the RTOG Pain and Narcotic Scale Karnofsky performance scale ≥ 60 Defined haematological and laboratory criteria Previous endocrine therapy and RT acceptable Written informed consent.</p>
<p>Exclusion criteria: -</p>
<p>Population: Number of patients = 142.</p>
<p>Interventions: Five doses of RT at a daily dose of 2.5 Gy: 10 Gy (x 4 fractions) n = 37 (incl. 1 ineligible) 12.5 Gy x 6 fractions n = 23 15 Gy (x 6 fractions) n = 18 17.5 Gy (x 7 fractions) n = 40 (incl. 1 ineligible) 20 Gy (x 8 fractions) n = 26 Shielding reduced the exposure of the lungs to not more than 6 Gy or 15 Gy to the liver/kidneys</p>
<p>Outcomes: Toxicity Time to progression Overall survival</p>
<p>Follow up: Blood counts were repeated weekly (or until normal) following HBI then every 3 months. Bone scans, KPS assessments, history, pain and narcotic scores were recorded every 3 months for the first year and then 6-monthly.</p> <p>125/142 patients died by the study end. Median follow-up = 9.4 months (range: 0.6-60 months).</p>
<p>Results: Treatment arms were similar in most respects except for KPS.</p> <p>Adverse events (10 Gy/12 Gy/15 Gy/17.5 Gy/20 Gy): 31/120 patients who completed their treatment experienced grade 3/4 adverse events: Anaemia: (4/0/1/3/3) Leukopenia: (5/2/3/6/5) Thrombocytopenia: (3/2/1/5/5) GI: (2/2/0/2/2) Lung: 0/0/0/0/0 (1 patient had a grade 5 (fatal) pulmonary toxicity) There were no dose-limiting, non-haematological toxicities at any dose.</p> <p>Time to new disease in the HB field: There was no difference in failure % after 17.5 Gy (19%) compared to 10 Gy (19%) at 12 months and after 18 months the rate is slightly better (19% versus 25%) but not significant.</p> <p>Time to new treatment (RT) in the HB field: The percentage failure increases with decreasing doses of HBRT, as would be expected. At 1 year, for example, the time to RT for patients after 10 Gy HBRT is 36% compared with 19% for</p>

patients that had received 20 Gy HBRT. At 18 months these figures are, respectively, 42% versus 30%.

Survival:

This was not an endpoint in the study but was partially reported. At 12 months, 41% patients who had received 10 Gy and 12.5 Gy fractionated HBRT were alive, compared with 44% after 15 Gy or 17.5 Gy. Initially survival was better for those patients having received 20 Gy than lower doses, but by 2yrs this advantage had been lost.

General comments:

This paper is primarily reporting results of a multi-centre, dose searching phase I trial of fractionated hemi-body irradiation but also reports some of the resultant haematological and other toxicities, time to progression and some survival data. The study spans 1989-1993 and the data were analysed in 1995.

41/142 (29%) patients were female. It is not stated whether any of the males had breast cancer.

Eligibility was confirmed by telephone call whereupon patients were assigned to treatment sequentially to one of five different dose regimes.

According to previously established criteria, the authors concluded the maximum tolerable dose of HBRT, with the least toxicity, was 17.5 Gy delivered in 2.5 Gy fractions.

Updated evidence (6.4)

Summary

There were two papers identified to update the evidence on the management of bone metastases in patients with advanced breast cancer. Ha *et al.* (2007) presented a meta-analysis of RCTs that investigated oral clodronate treatment for women with breast cancer compared with placebo or no treatment and found no significant difference between study arms in terms of bone metastasis-free survival, disease-free survival or non-skeletal metastasis-free survival.

Gagnon *et al.* (2007) presented results from a matched pair analysis of treatment with stereotactic radiosurgery after disease progression following external beam radiotherapy compared with patients who had received external beam radiotherapy alone. The authors found no differences between groups for mobility, performance status, pain or survival and concluded that equivalence in outcomes denoted a successful strategy for treating patients with radiosurgery who had already been treated with conventional radiotherapy and may have few treatment options left.

References

Ha, TC and Li, H (2007) Meta-analysis of clodronate and breast cancer survival. *Br J Cancer* **96** (12): 1796-1801

Gagnon GJ., Henderson FC., Gehan EA., Sanford D., Collins BT., Moulds JC and Dritschilo A (2007) Cyberknife radiosurgery for breast cancer spine metastases: a matched-pair analysis. *Cancer* **110**: 1796-1802

Evidence tables

Question: The management of bone metastases

Created by: Karen Francis on 22/17/2008

Ha *et al.* (2007)

<p>Design: Meta analysis of randomised controlled trials (therapy). Evidence level: 1+ Country: Multi-national</p>
<p>Inclusion criteria: Included study participants: Patients with histologically or cytologically proven breast cancer No prior history of other malignant diseases (besides recurrent breast cancer) No bisphosphonate use Included patients with early, advanced and metastatic breast cancer (actual numbers unknown)</p> <p>Included papers: RCTs that investigated (bone metastasis-free or non-skeletal metastasis-free) overall survival among breast cancer patients receiving oral clodronate vs placebo or no treatment.</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 1,653 with early breast cancer and 503 with advanced disease. Median ages ranged from 51 to 61 years across studies</p>
<p>Interventions: Oral clodronate at 1600 mg per day given for either 2 or 3 years compared with an identical placebo or no treatment.</p>
<p>Outcomes: Disease-free survival (DFS), 5-year (bone metastasis-free and non-skeletal metastasis-free) overall survival (OS)</p>
<p>Follow up: -</p>
<p>Results: Disease-free survival: There was no evidence to suggest that clodronate therapy improves overall, non-skeletal metastasis free survival or bone metastasis-free survival significantly in either group of patients.</p> <p>Pooled analysis did not find any statistically significant difference in the time to appearance of bone metastasis in advanced breast cancer patients who received adjuvant clodronate treatment compared with those who did not (HR = 0.68) (95%CI: 0.23-1.98).</p> <p>There was no statistically significant delay in the occurrence of non-skeletal metastases between advanced breast cancer patients receiving adjuvant clodronate therapy and those receiving no treatment (HR = 0.95) (95%CI: 0.31-2.91). These data were derived from four trials, three of which included only patients with early breast cancer however, in the fourth trial the number of patients was 647.</p> <p>Overall survival: The pooled results demonstrated no statistically significant difference in OS between patients treated with adjuvant clodronate therapy and those receiving no treatment (HR = 0.73) (95%CI: 0.46-1.14)</p>
<p>General comments: This paper presents the findings of a systematic review of eight RCTs comparing oral clodronate therapy with placebo or no treatment. Five of the eight studies involved patients with advanced breast cancer whilst the remainder were women receiving clodronate as adjuvant therapy for early disease.</p> <p>Potential limitations exist with this meta-analysis since there were notable differences between</p>

studies with respect to survival data, there are mixed results in the reporting of publication bias and because of the limited availability, quality and heterogeneity of included studies. However, the authors concluded that they had found no evidence of any statistically significant difference in overall survival, bone metastasis-free survival or non-skeletal metastasis-free survival in advanced breast cancer patients receiving clodronate compared with placebo or no treatment.

Gagnon *et al.* (2007)

Design: Retrospective case control study (therapy). Evidence level: 2-
Country: United States of America

Inclusion criteria:

Women \geq 18 years of age
Histologically or cytologically confirmed spinal metastases from breast cancer

Exclusion criteria:

None stated

Population:

Number of patients = 35. Age range:

Interventions:

[1] SR group (n=17): Stereotactic radiosurgery (SR) treatment with 3 x 800 cGy (in the case of no prior radiation to the site) or 3 x 700 cGy (for patients who had received prior radiation to that spinal level)

[2] CRT group (n=18): external beam radiotherapy (RT) (given between 1995 and 2005)

Outcomes:

Mobility, performance status and pain. Overall survival (OS).

Follow up:

At the time of publication 8 SR patients and 15 CRT patients had died.

Results:

Ambulatory scores did not differ between groups over the first 24 months of the study. Whilst performance scores declined in both groups significantly over time, there was no difference between them over the first 24 months. Pain decreased significantly in both groups with time but, again, there was no significant difference between the groups in this respect.

There was no significant difference in survival between the SR and CRT patients but median values were not reported and cannot be derived from the data presented.

General comments:

This paper describes a retrospective series of women who had been treated at a single hospital for spinal metastases from breast cancer. Patients had progressive disease after receiving external beam radiotherapy (RT) and were treated with CyberKnife stereotactic radiosurgery.

Matched pair analyses were used to compare outcomes, the controls being selected amongst patients who had received conventional external beam therapy for spinal metastases. Patients were matched based primarily on the time to diagnosis of metastases from the original diagnosis. Secondary considerations included presence or absence of visceral metastases, stage at diagnosis, endocrine receptor status, prior RT to breast or chest wall and prior chemotherapy. The non-matching factor was previous RT to the spinal area which was distributed almost uniformly in the SR group. There were few significant differences between groups at baseline except that more patients in the CRT group had pain after the diagnosis of metastases (P = 0.01).

There were no significant differences observed between the treatment groups for mobility, performance status, pain or survival. The authors conclude that equivalence in outcomes denotes a successful strategy for treating patients with radiosurgery who had already been treated with RT and may have few treatment options left.

Health Economic Summary

Short Summary

Six papers were selected from the original list of 959 papers identified from the search of economic evidence. Despite the numerous interventions identified for this topic, all six papers referred to the use of bisphosphonates in the prevention of skeletal related events. There was no economic evidence on the use of bisphosphonates for pain relief. None of the studies compared all the bisphosphonates against each other; instead they were either individually compared against no treatment or compared against a limited number of alternatives. All presented cost-utility analyses, four of which were undertaken in a UK setting, the other two in America and Canada.

One of the six papers in the review is a Health Technology Assessment report (Ross et al, 2004). This report presents an economic review of the (then) published literature, and also a model which estimates the cost-effectiveness of pamidronate in the treatment of hypercalcaemia and prevention of skeletal morbidity. Although the report is not limited to breast cancer specifically, it does report findings in patients with breast cancer separately, and on that basis is included in this review. The HTA report has the advantage that it is an independent analysis, unlike the other three UK economic papers.

The model built for the HTA report (Ross et al, 2004) considers costs from both a hospital and social care perspective. The report indicates that the community care costs associated with fracture care might be considerable and if omitted might substantially underestimate the cost-effectiveness of bisphosphonates. The authors conclude that the use of pamidronate is highly cost-effective (£1,300 per QALY compared to no treatment) in the prevention of skeletal morbidity in patients with breast cancer and skeletal metastases, and that it may be cost-saving when fracture care, and/or other variables are taken into account. Despite the basecase analysis yielding a favourably low incremental cost-effectiveness ratio, the results are subject to a high degree of uncertainty. In their analysis the base case cost-effectiveness result is sensitive to bisphosphonate cost, event rate and events costs but no sensitivity analysis on the cost-utility analysis is made explicit. They do present a one-way sensitivity analysis on the cost-effectiveness analysis showing the worst case scenario ranges from cost-saving to a incremental cost per skeletal related event per patient averted is 53 times higher than the baseline result. If we apply this to the baseline cost-utility estimate of £1,380 per QALY, bisphosphonates could range from being cost-saving to £73,140 per QALY.

The most recent study, Botteman et al 2006, uses many of the assumptions employed by Ross et al 2004, but updates the costs used and incorporates results of a recent zoledronic acid vs. placebo trial. The authors conclude that zoledronic acid dominates other bisphosphonates (it is both less costly and more effective), although it should be noted that this study includes authors employed by the manufacturers of zoledronic acid. De Cock et al on the other hand, in their two papers (chemotherapy treated patients 2005a, and hormone therapy patients 2005b) both of which include authors from the manufacturer of ibandronate, infer that oral ibandronate dominates i.v. zoledronic acid and i.v. pamidronate.

The North American studies reported very different levels of cost-effectiveness (range CAN\$18,000 to US\$305,000 per QALY). These ratios imply that bisphosphonates may not be cost effective compared to no treatment in a North American context.

The economic modelling from a UK NHS and social services perspective conducted in the studies included in this review indicates that use of bisphosphonates in the management of bone metastases from breast cancer appears to be cost-effective. However the papers reviewed show conflicting evidence over which of the bisphosphonates is most cost-effective. Since bisphosphonates as a class of drugs seem to be highly cost-effective, further independent analysis was not considered a high priority.

Full Evidence Summary

Despite the numerous technological interventions identified as part of topic 18, “the management of metastatic bone disease”, economic evidence was found only for bisphosphonates. Furthermore, these studies did not distinguish between the three patient populations {(a) patients with solitary bone metastasis; (b) patients with multiple bone metastases as only apparent disease site; (c) patients with multiple bone metastases as part of more widespread disease}.

Six papers were eventually selected from an original hit list of 959 papers. All six of the selected economic analyses present cost-utility (cost per QALY) analyses using modelling techniques. Four of the six economic analyses have a UK setting, one is Canadian (Dranitsaris et al, 1999), and one is American (Hillner et al, 2000). Key features of the analyses are presented in the summary table below.

The review includes a Health Technology Assessment report (Ross et al, 2004). This report presents an economic review of the then published literature, and also a model to estimate the cost-effectiveness of pamidronate in the treatment of hypercalcaemia and prevention of skeletal morbidity. Although the report is not limited to breast cancer specifically, it does report breast cancer findings separately, and on that basis is included in this review. The HTA report has the advantage that it is an independent analysis, unlike the other three UK economic papers.

Pre- HTA report

The HTA literature review includes the analyses presented by Dranitsaris, 1999 and Hillner 2000. Although direct cross country comparisons of economic analyses should not be made, these studies reported very different levels of cost-effectiveness (range CAN\$18,000 to US\$305,000 per QALY). These ratios imply that bisphosphonates may not be cost effective compared to no treatment in a North American context. Dranitsaris and Hsu estimated 0.15 QALYs gained, but Hillner and colleagues only 0.037 (chemotherapy group) or 0.025 (hormonal group). The reason for this difference is unclear but the fact that Hillner and colleagues ascribed a reduced quality of life only for the month in which the SRE occurs might suggest that they are underestimating the gains associated with preventing events. It is not clear how long the estimated duration of an SRE is in the Dranitsaris and Hsu model. Other differences were the 50% lower cost of bisphosphonate therapy in the Canadian study, and their assumption that all non-vertebral fractures were assumed to be hospitalised, both of which improve cost-effectiveness. The difference in the results indicates an inherent sensitivity of the ICER to these modelling assumptions.

HTA report

The model built in the HTA report (Ross et al, 2004) considers costs from both a hospital and social care perspective, rather than a simple hospital perspective of its North American predecessors. The HTA report indicates that the community care costs associated with fracture care “might be considerable”. As the authors explain, “omission of the costs of social care, be it provided by the family, the community health service or the social services, might substantially underestimate the cost savings to society associated with bisphosphonate therapy”. Ross et al concluded that the use of pamidronate was cost-effective (£1,300 per QALY compared to no treatment) in the prevention of skeletal morbidity in patients with breast cancer and skeletal metastases, and that it may be cost-saving when fracture care, and/or other variables are taken into account. This result was however sensitive to treatment effect assumption and is likely to give a borderline cost-effective result at the lower confidence limit.

Post-HTA report

The literature post-HTA report (all UK studies) all show bisphosphonate therapy to be cost-effective, but disagree as to which therapy is most cost-effective. The most recent study, Botteman et al 2006, uses many of the assumptions employed by Ross et al 2004 in the HTA report, but updates the costs used and incorporates results of a recent zoledronic acid vs. placebo trial. The authors conclude that zoledronic acid dominates other bisphosphonates (both less costly and more effective), although it should be noted that this study includes authors employed by the manufacturers of ZA. De Cock et al on the other hand, in their two papers (chemotherapy treated patients 2005a, and hormone therapy patients 2005b) both of which include authors from the manufacturer of ibandronate, infer that oral ibandronate dominates i.v. zoledronic acid and i.v. pamidronate.

Summary table

Setting	Rx of interest	Comparator	Results – cost per patient			Results – effectiveness per patient			Results – incremental cost-effectiveness			
			Net lifetime costs (vs. no therapy), £			QALY gains (vs. no therapy)			Cost per QALY, £			
			1 st analysis ^a	2 nd analysis ^b	1 st analysis	2 nd analysis	1 st analysis	2 nd analysis	1 st analysis	2 nd analysis		
Botteman et al, 2006	UK	OI, IBN, ZA, PA, OC	NT	ZA	-2,267	1,949	ZA	0.205	0.190	ZA	dominant	dominant
				PA	113	883	PA	0.194	0.186	PA	584	dominant
				IBN	458	1,085	IBN	0.193	0.177	IBN	2,370	6,126
				OI	-2,114	n/a	OI	0.185	n/a	OI	dominant	n/a
				OC	n/a	-450	OC	n/a	0.104	OC	n/a	dominant
Ross et al, 2004	UK	PA	NT	Incremental cost of PA therapy over 48 months: £444 per patient			Additional QALYs from PA therapy (vs. no therapy): 0.33 QALYs			Cost per QALY: = £1340		
De Cock et al, 2005a	UK	OI	ZA, PA	Total lifetime cost per patient: (receiving chemotherapy) OI = £7,693; ZA = £8,079; PA = £7,917			Additional QALYs (vs. no therapy): OI = 0.477 QALYs; ZA = 0.458 QALYs; PA = 0.457 QALYs			OI dominates ZA and PA.		
De Cock et al, 2005b	UK	OI	ZA, PA	Total lifetime cost per patient: (receiving hormonal therapy) OI = £7,700 ZA = £8,008 PA = £7,858			Additional QALYs (vs. no therapy): OI = 0.477 QALYs; ZA = 0.459 QALYs; PA = 0.458 QALYs			OI dominates ZA and PA.		
Hillner et al, 2000	USA	PA	NT	Total net costs over 24 months: Patients receiving chemotherapy: PA = \$17,906; NT (placebo) = \$13,938. Patients receiving hormonal therapy: PA = \$20,319, No therapy (placebo) = \$12,634			Additional QALYs from PA therapy (vs. no therapy): 0.037 QALYs (for patients receiving chemotherapy) 0.026 QALYs (for patients receiving hormonal therapy)			Cost per QALY: \$108,200 (for patients receiving chemotherapy) \$305,300 (for patients receiving hormonal therapy)		
Dranitsaris & Hsu, 1999	Canada	PA	NT	Health care utilization cost per patient over 12 months: Pamidronate = CAN\$9,180, No therapy (placebo) = CAN\$6,380			Additional QALYs from PA therapy (vs. no therapy): 0.15 QALYs			Cost per QALY = CAN\$18,700		

SRE = skeletal related events; NT = no treatment; ZA = zoledronic acid; PA = pamidronate; IBN = i.v. ibandronate; OI = oral ibandronate; OC = oral clodronate; QALY = quality adjusted life year
^a using Anderson-Gill hazard ratios; ^b using the skeletal morbidity rate (SMR)

Note. A dominant treatment option is one which is both more effective, and less costly than its comparator(s).

In conclusion, economic modelling in the context of the UK NHS and social services perspective indicates that use of bisphosphonates in the management of bone metastases from breast cancer appears to be cost-effective. This result appears to be robust to most univariate sensitivity analyses, although there are scenarios in the HTA report which imply that Pamidronate is not always cost-effective. Results of modelling in the North American context indicate that bisphosphonates may not be cost-effective. There is lack of clarity over which of the bisphosphonates is most cost-effective.

References

Botteman, M., V. Barghout, et al. (2006). "Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases." *Ann Oncol* 17(7): 1072-1082.

De, C. E., J. Hutton, et al. (2005). "Cost-effectiveness of oral ibandronate compared with intravenous (i.v.) zoledronic acid or i.v. generic pamidronate in breast cancer patients with metastatic bone disease undergoing i.v. chemotherapy." *Support Care Cancer* 13(12): 975-986.

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Hillner, B. E., J. C. Weeks, et al. (2000). "Pamidronate in prevention of bone complications in metastatic breast cancer: a cost-effectiveness analysis." *J Clin Oncol* 18(1): 72-79.

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Evidence tables

Question: Are treatments for the management of metastatic bone disease in breast cancer patients cost-effective?

Created by: Sarah Willis on 04/01/07 (updated on 16/07/08)

Full bibliographic reference	<i>Botteman, M., V. Barghout, et al. (2006). "Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases." Ann Oncol 17(7): 1072-1082.</i>
Source of funding	Not stated, however two of the authors are from Novartis (manufacturers of zoledronic acid).
Economic study type	Cost-effectiveness study using a Markov model to assess the cost and quality of life benefits associated with five bisphosphonates vs. no therapy.
Population, country & perspective	Patients with breast cancer and bone metastases. UK, NHS perspective.
Comparison(s)	Placebo, oral ibandronate (OI), i.v. ibandronate (IBN), zoledronic acid (ZA), generic pamidronate (PA), generic oral clodronate (OC)
Source of effectiveness data	<ul style="list-style-type: none"> ▪ Patients receiving no therapy assumed to experience 3.05 SREs a year – the pooled average rate of SREs observed in placebo group of bisphosphonate trials (Kohno et al, 2005; Body et al, 2003; Lipton et al, 2000; Paterson et al, 1993) ▪ Effectiveness of pamidronate – (Rosen, 2003; Lipton et al, 2000) ▪ Effectiveness of zoledronic acid (Kohno et al, 2005) ▪ Effectiveness of i.v. ibandronate (Tripathy et al, 2004; Body et al, 1999) ▪ Effectiveness of generic oral clodronate – (Paterson et al, 1993)
Cost components	UK £ Stirling. Price year not reported. Included: <i>SRE-related costs</i> - average hospital cost associated with an SRE (updated figure from Ross et al 2004), monthly cost of bone pain (Ross et al 2004), community care costs (of 3 month duration) for patients with pathological long-bone fractures. <i>Cost of bisphosphonate therapy</i> - drug costs (BNF 49, 2005), clinical staff time (DesHarnais et al 2001), supply and lab testing costs. Also included a one-hour medical consultant visit for all patients initiating a 2nd line therapy.

	Excluded: none stated		
Time horizon, discount rate	10 years. 3.5% discount rate for both costs and benefits, in accordance with NHS economic research guidelines		
Results – cost	Lifetime SRE-related cost (with no therapy) = £18,662.		
	Net costs (vs. no therapy):		
		Primary analysis (using Anderson-gill hazard ratio)	Secondary analysis (using SMR ratio)
	ZA	-£2,267	£1,949
	PA	£113	£883
	IBN	£458	£1,085
	OI	-£2,114	n/a
	OC	n/a	-£450
Results – effectiveness	QALY gains (vs. no therapy):		
		Primary analysis (using Anderson-gill hazard ratio)	Secondary analysis (using SMR ratio)
	ZA	0.205	0.190
	PA	0.194	0.186
	IBN	0.193	0.177
	OI	0.185	n/a
	OC	n/a	0.104
Results – adverse events	The quality of life and economic impact related to drug-induced severe adverse events were not included in the model given the rarity of such events.		
Results – incremental cost-effectiveness	ZA is found to be the dominant treatment option (incl. no treatment) in a secondary analysis calculating the net monetary benefit, at a threshold value of £30,000 per QALY.		
	Also presented are the cost per QALY values for each treatment option vs. no treatment:		
		Primary analysis (using Anderson-gill hazard ratio)	Secondary analysis (using SMR ratio)
	ZA	dominant	dominant
	PA	584	dominant
	IBN	2,370	6,126
	OI	dominant	n/a
OC	n/a	dominant	
Results-uncertainty	<p>Both univariate and multivariate sensitivity analyses were carried out.</p> <p>The univariate sensitivity analyses show the parameters that have the greatest impact are the skeletal morbidity rate (SMR) in no therapy, the cost of a skeletal-related event (SRE) and median survival. Although they do not present the results, the authors note that the choice of utility inputs can have a profound impact on the results. The ranking of therapy preference remained unchanged except in one scenario in each analysis: admin time for IBN = admin time for ZA, IBN became more attractive than PA.</p> <p>Multivariate analysis was performed for which several parameters were varied simultaneously. Acceptability curves are presented for various willingness to pay values (ranging from £0 to £100,000). At a willingness to pay threshold of £30,000 per QALY, ZA is the preferred option in 51% of the simulations and all bisphosphonates appear to be cost-effective in 97% of the simulations.</p>		
General comments	As a group, all bisphosphonates for the prevention of skeletal related events in UK breast cancer patients with bone metastases are either cost-saving or at least highly cost effective compared to no therapy. All bisphosphonates were cost-effective vs. no therapy (cost per QALY £2,400 or less in the primary analysis using Anderson-Gill hazard ratios, £6,100 per QALY in the secondary analysis using the SMR ratio). ZA dominates the other bisphosphonates considered in the analyses (that is, it is both less expensive and more effective than NT, PA, OI and OC).		

Full bibliographic reference	Ross, J. R., Y. Saunders, et al. (2004). "A systematic review of the role bisphosphonates in metastatic disease." Health Technology Assessment 8(4): iii-139.
Source of funding	HTA
Economic study type	Cost-effectiveness and cost-utility analysis using markov modelling.
Population, country & perspective	UK. NHS and social care perspective for breast cancer patients with bone metastases.
Comparison(s)	Pamidronate (90mg) vs. no treatment
Source of effectiveness data	<ul style="list-style-type: none"> ▪ Median survival (from placebo arm) – 18 months (Lipton et al, 2000; Hultborn et al, 1999) ▪ (No bisphosphonate arm) monthly incidence of SREs (vertebral fracture, non-vertebral fracture, hypercalcaemia, RT and orthopaedic surgery) (Lipton et al, 2000) ▪ (Bisphosphonate arm) monthly incidence of SREs for no-bisphosphonate arm multiplied by an estimated relative risk which was calculated for each SRE by random effects meta-analysis. ▪ Reduction in bone pain (1 in 7 patients would have bone pain fully alleviated each month) (Wong and Wiffen, 2002) ▪ QALY estimates (Dranitsaris and Hsu, 1999) – adjusted to account for a longer treatment duration
Cost components	<p>UK £ Stirling. Cost year 2000/1.</p> <p>Included:</p> <p>(a) cost to the hospital of providing bisphosphonate therapy;</p> <p>(b) inpatient and outpatient hospital costs associated with treating SREs, fractures, hypercalcaemia, surgery and RT;</p> <p>(c) community health service costs associated with palliation of bone pain;</p> <p>(d) community health service costs associated with the longer term care of patients;</p> <p>Excluded:</p> <p>Costs to patients and their families were not included in line with the costing perspective taken.</p>
Time horizon, discount rate	<p>48 months (to be consistent with the longest time horizon of the studies examined in the literature).</p> <p>Costs - 6%, benefits 1%. Also investigate use of different discount rates in sensitivity analysis. The results are not sensitive to the discount rates.</p>
Results – cost	The incremental cost of bisphosphonate use was estimated to be £444 per patient.
Results – effectiveness	It was estimated that for every 100 patients treated with bisphosphonates (pamidronate), 179 SREs would be averted – 54 non-vertebral fractures, 16 vertebral fractures, 34 episodes of hypercalcaemia, 64 episodes of RT and 12 episodes of surgery.
Results – adverse events	The cost of treating side-effects from the drug was not included because of the rarity of serious side-effects. The cost of treating SCC was not estimated because there is not good evidence of a reduction in incidence associate with the use of bisphosphonates.
Results –incremental cost-effectiveness	It was estimated that the use of bisphosphonates in this context costs £250 per SRE averted or £1645 per fracture avoided. Incremental cost per QALY gained was £1340.
Results-uncertainty	Univariate sensitivity analyses were performed. The results were not sensitive to the survival rate, the inclusion of SCC or the assumption of constant event rates. Costs and cost-effectiveness were sensitive to the price of bisphosphonates, the probability of averting an event and the unit costs associated with events. Whilst the incremental cost per SRE averted in the baseline analysis is £250, the results of the sensitivity analysis show the cost per SRE averted could lie anywhere between being cost-saving and costing £13,153. The most sensitive parameter was the relative risk of SREs which, using the higher confidence limit of this value, represent a cost of £7,383 per SRE averted.

	In a separate sensitivity analysis including an analysis of possible cost-savings from prevention of fracture, the authors conclude that inclusion of such savings may mean that use of pamidronate is cost-saving to the NHS.
General comments	This analysis is the most relevant for this guideline in that it takes a UK NHS and social care perspective and is the most independent assessment of the UK economic appraisals found as part of this review.

Full bibliographic reference	De, C. E., J. Hutton, et al. (2005). "Cost-effectiveness of oral ibandronate compared with intravenous (i.v.) zoledronic acid or i.v. generic pamidronate in breast cancer patients with metastatic bone disease undergoing i.v. chemotherapy." Support Care Cancer 13(12): 975-986.
Source of funding	Not stated, however two of the authors are from Roche (manufacturers of ibandronate)
Economic study type	Cost-utility analysis (results presented as cost per QALY)
Population, country & perspective	Patients with metastatic bone disease from breast cancer receiving i.v. chemotherapy
Comparison(s)	Oral ibandronate (50mg) compared with i.v. zoledronic acid and i.v. pamidronate (90mg)
Source of effectiveness data	<ul style="list-style-type: none"> ▪ Relative risk reduction rates for SREs (Body et al 2004; Lipton et al 2000) ▪ Assumed ZA and OI are equally effective in preventing SREs. ▪ Baseline average utility value = 0.40 (1 month without an SRE) (Van Hout et al, 1994) ▪ Duration of an SRE = 1 month (Hillner et al, 2000) ▪ Reduction in bone pain: <ul style="list-style-type: none"> ○ Assumed OI associated with utility value of 0.424 (as reported in phase III trial, Tripathy et al, 2003) ○ Assumed no reduction in pain with ZA or PA ▪ Reduction in analgesic use: 7% for OI (Body et al, 2004a; Tripathy et al. 2003); 3% for both ZA and PA (Berenson et al, 2001; Rosen et al, 2001; Lipton et al 2000; Fulfaro et al 1998)
Cost components	Included: Resource use and staff time: From a US microcosting study (DesHarnais et al) validated by UK clinician. Unit costs: SRE management, i.v. bisphosphonate administration, lab tests, renal impairment/failure, drug acquisition.
Time horizon, discount rate	UK £ Stirling. Price year not stated. Time horizon: mean average survival (14.3 months) Discount rate was not stated.
Results – cost	Total lifetime cost per patient: OI = £7,693 ZA = £8,079 PA = £7,917
Results – effectiveness	QALYs per patient per alternative were not stated. However, incremental QALYs compared to no therapy were presented, as below: OI = 0.477 QALYs; ZA = 0.458 QALYs; PA = 0.457 QALYs
Results – adverse events	<ul style="list-style-type: none"> ▪ Included drug-related renal toxicity at 5% for ZA (Body et al, 2004b; Ibrahim et al, 2003; Rosen et al, 2001) ▪ No additional risk of drug-related renal impairment or failure was assumed for oral ibandronate (Diel, 2003). ▪ No additional risk of drug-related renal impairment or failure was assumed for i.v. pamidronate (supported by clinical opinion)
Results –incremental cost-effectiveness	OI dominates ZA and PA.
Results-uncertainty	Both one-way and probabilistic sensitivity analyses were performed. Parameters varied included survival, utility values, 100% compliance and continuation, staff time for infusions and SRE treatment costs. The results remained cost-effective vs. the comparators given a £30,000 per QALY threshold. Using pairwise comparisons, the cost-effectiveness acceptability curves showed that at a

	cost per QALY of £30,000, OI was the cost-effective strategy in 85% of simulations vs. ZA and 79% of simulations vs. PA.
General comments	It should be noted that no efficacy data of ZA vs. placebo were available at the time of this analysis. This meant the authors assumed the same SRE relative risk reduction for zoledronic acid as used for oral ibandronate.

Full bibliographic reference	De, C. E., J. Hutton, et al. (2005). "Cost-effectiveness of oral ibandronate versus IV zoledronic acid or IV pamidronate for bone metastases in patients receiving oral hormonal therapy for breast cancer in the United Kingdom." Clin Ther 27(8): 1295-1310.
Source of funding	Not stated, however two of the authors are from Roche (manufacturers of ibandronate)
Economic study type	Cost-utility analysis (results presented as cost per QALY)
Population, country & perspective	Patients with metastatic bone disease from breast cancer receiving oral hormonal therapy. UK. NHS perspective.
Comparison(s)	Oral ibandronate (50mg) compared with i.v. zoledronic acid and generic pamidronate i.v. (90mg)
Source of effectiveness data	<ul style="list-style-type: none"> ▪ Relative risk reduction rates for SREs (Body et al, 2004; Body et al, 2003; Hillner et al, 2000; Lipton et al, 2000) ▪ Assumed ZA and OI are equally effective in preventing SREs. ▪ Baseline average utility value = 0.40 (1 month without an SRE) (Van Hout et al, 1994) ▪ Duration of an SRE = 1 month (Hillner et al, 2000) ▪ Reduction in bone pain: <ul style="list-style-type: none"> ○ Assumed OI associated with increase of 5% in utility (as reported in phase III trial, Tripathy et al, 2003) ○ Assumed no reduction in pain with ZA or PA ▪ Reduction in analgesic use: 7% for OI (Body et al, 2004a; Tripathy et al. 2003); 3% for both ZA and PA (Berenson et al, 2001 Rosen et al, 2001; Lipton et al 2000; Fulfaro et al 1998)
Cost components	<p>Included: Direct health care costs - staff time and supplies for bisphosphonate infusions from a US microcosting study. Unit costs reported separately: SRE management, i.v. bisphosphonate admin (personnel time supplied), lab tests, renal impairment/failure, pain management, drug acquisition.</p> <p>Excluded: Transport costs of taking patients to radiotherapy dept</p>
Time horizon, discount rate	Time horizon: mean average survival (14.3 months) No discount rate was stated.
Results – cost	UK £ Stirling. Price year not stated. <i>Total lifetime cost per patient:</i> OI = £7,700 ZA = £8,008 PA = £7,858
Results – effectiveness	QALYs per patient per alternative were not stated. However, incremental QALYs compared to no therapy were presented, as below: OI = 0.477 QALYs ZA = 0.459 QALYs PA = 0.458 QALYs
Results – adverse events	<ul style="list-style-type: none"> ▪ Included drug-related renal toxicity at 5% for ZA (Body et al, 2004b; Ibrahim et al, 2003; Rosen et al, 2001) ▪ No additional risk of drug-related renal impairment or failure was assumed for oral ibandronate (Diel, 2003). ▪ No additional risk of drug-related renal impairment or failure was assumed for i.v. pamidronate (supported by clinical opinion)
Results –incremental cost-effectiveness	OI dominates ZA and PA.

Results-uncertainty	<p>Both one-way and probabilistic sensitivity analyses were performed.</p> <p>Parameters varied included survival, utility values, 100% compliance and continuation, staff time for infusions and SRE treatment costs. The results remained cost-effective vs. the comparators given a £30,000 per QALY threshold.</p> <p>Using pairwise comparisons, the cost-effectiveness acceptability curves showed that at a cost per QALY of £30,000, OI was the cost-effective strategy in ≥82% of simulations vs. ZA and ≥79% of simulations vs. PA.</p>
Comments	<p>It should be noted that no efficacy data of ZA vs. placebo were available at the time of this analysis. This meant the authors assumed the same SRE relative risk reduction for zoledronic acid as used for oral ibandronate.</p>

Full bibliographic reference	Hillner, B. E., J. C. Weeks, et al. (2000). "Pamidronate in prevention of bone complications in metastatic breast cancer: a cost-effectiveness analysis." <i>J Clin Oncol</i> 18(1): 72-79.
Source of funding	Supported in part by a faculty research award from the American Cancer Society.
Economic study type	cost-utility and cost-effectiveness analysis
Population, country & perspective	Hypothetical group of women with metastatic breast cancer with one or more osteolytic lesions at least 1cm in diameter. All women received systemic therapy. The setting for the analysis is the USA and the perspective purports to be societal, although the costs included do not suggest this was the approach taken (see cost component section below).
Comparison(s)	i.v. pamidronate (90mg) vs. no therapy (placebo)
Source of effectiveness data	The two Aredia Breast Cancer Study Group Protocol trials 18 and 19 (Theriault et al, 1999; Hortobagyi et al, 1998; Hortobagyi et al. 1996). Each protocol was an international, multi-centre, randomized, double-blind, parallel trial.
Cost components	<p>US dollars. Price year not reported.</p> <p>Included: Direct health care costs (incl. radiation therapy and related surgery costs) and direct non-medical costs for 14 half days of lost work for a companion to accompany the patient for therapy (\$50 per half day)</p> <p>Excluded: not stated</p>
Time horizon, discount rate	<p>24 months.</p> <p>"Because the timing of individual SREs was not available, discounting of costs and benefits was not performed - given the short life expectancy of women with metastatic breast cancer the discount rate is likely to have little effect on these results." (Hillner et al, 2000: 75)</p>
Results – cost per patient per alternative	<p>Total net costs over 24 months:</p> <p><i>Patients receiving chemotherapy:</i></p> <p>PA = \$17,906;</p> <p>NT (placebo) = \$13,938.</p> <p><i>Patients receiving hormonal therapy:</i></p> <p>PA = \$20,319,</p> <p>No therapy (placebo) = \$12,634</p>
Results – effectiveness per patient per alternative	<p>Additional QALYs from PA therapy (vs. no therapy):</p> <p>0.037 QALYs (for patients receiving chemotherapy)</p> <p>0.026 QALYs (for patients receiving hormonal therapy)</p>
Results – adverse events	Not stated.
Results –incremental cost-effectiveness	<p>Cost per QALY:</p> <p>\$108,200 (for patients receiving chemotherapy)</p> <p>\$305,300 (for patients receiving hormonal therapy)</p>

Results-uncertainty	Carried out one-way sensitivity analysis. Symptomatic events: conducted analyses in which costs and reduced QoL were limited to SREs requiring active therapy (ie. Removing disutility from asymptomatic SREs) -- less cost-effective £134,700 per QALY. Hypercalcaemia: excluding hypercalcaemia as an SRE -- cost-effectiveness ratio almost doubles to \$187,900 per QALY QoL values: if true of adverse quality of life associated with symptomatic SREs was greater than 1 month, then the model may have underestimated the benefit of avoiding SREs. Analysis using a 2 month length of an SRE led to £77,300 per QALY.
Comments	These results are not cost-effective. The key differences from the Canadian study are higher costs of bisphosphonates, lower gains in health related quality of life due to smaller HR utility benefits, and shorter periods of benefit.

Full bibliographic reference	Dranitsaris, G. and T. Hsu (1999). "Cost utility analysis of prophylactic pamidronate for the prevention of skeletal related events in patients with advanced breast cancer." Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 7(4): 271-279.
Source of funding	Novartis
Economic study type	Cost-utility analysis using a decision analytic model
Population, country & perspective	Patients with metastatic breast cancer receiving chemotherapy. Canadian health care system perspective.
Comparison(s)	i.v. pamidronate (90mg) vs. no therapy (placebo)
Source of effectiveness data	Used the only available randomized, double-blind, placebo-controlled trial of pamidronate in patients with metastatic breast cancer receiving chemotherapy, (Hortobagyi et al, 1996).
Cost components	Canadian dollars. Price year not stated. Included: <ul style="list-style-type: none"> ▪ Drug costs (supplied by Novartis Pharma Canada) ▪ Treatment costs (patient admission, drug preparation, i.v. administration) ▪ Diagnostic costs (imaging, lab tests) ▪ Cost of treating skeletal related events (severe hypercalcaemia, orthopaedic surgery, radiotherapy and non-surgical treatment of non-vertebral fractures) Excluded: none stated
Time horizon, discount rate	12 months. n/a (since analysis was only over a 1yr period)
Results – cost per patient per alternative	Health care utilization cost per patient over 12 months: Pamidronate = CAN \$9,180, No therapy (placebo) = CAN \$6,380
Results – effectiveness per patient per alternative	Additional QALYs from pamidronate therapy (vs. no therapy): 0.15 QALYs (Preferences for alternative health states were determined using the Time Trade-Off (TTO) technique from a sample population of 25 Canadian women from the general public. These were compared with preferences ascertained from 25 female health professionals in the sensitivity analysis.)
Results – adverse events	Not stated.
Results – incremental cost-effectiveness	Cost per QALY = CAN \$18,700
Results-uncertainty	One-way sensitivity analysis carried out, investigating the effect of the following parameters: <ul style="list-style-type: none"> ▪ Excluding hypercalcaemia ▪ different SRE rates ▪ different costs for treating SREs (excl. surgery) ▪ health state preferences of health care professionals In all cases the incremental cost of pamidronate remained below CAN \$30,000 per QALY, except when surgical costs were excluded when the resulting cost per QALY gained was CAN \$32,100
Comments	Dranitsaris and Hsu, using a average 0.15 QALY gain per patient, found bisphosphonate treatment to be borderline cost-effective.

Drummond Checklist

Question	Botteman et al 2006	Ross et al 2004 (HTA report)	De Cock 2005a	De Cock 2005b	Hillner et al 2000	Dranitsaris et al 1999
1. The research question is stated.	Yes	Not fully	Yes	Yes	Yes	Yes
2. The economic importance of the research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes
3. The view point(s) of the analysis are stated and justified.	Yes	Yes	Yes	Yes	Not fully	Yes
4. The rationale for choosing the alternative programmes or interventions are stated.	Yes	Not fully	Not fully	Not fully	Yes	Yes
5. The alternatives being compared are clearly described.	Not clear	No	Yes	Yes	No	Yes
6. The form of economic evaluation is stated.	Not clear	No	Yes	Yes	No	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	No	No	Yes	Yes	No	No
8. The source(s) of effectiveness estimates are stated.	Yes	Yes	Yes	Yes	Yes	Yes
9. Details of the design and results of effectiveness study are given (if based on a single study).	No	Yes	No	No	Yes	Yes
10. Details of methods of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).	No	No	No	No	Not applicable	Not applicable
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	Yes	Yes	Yes	Yes
12. Methods to value health states and other benefits are stated.	Yes	Yes	Yes	Yes	Yes	Yes
13. Details from the subjects from whom valuations are obtained are given.	No	No	No	No	Yes	Yes
14. Productivity changes (if included) are reported separately.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
15. The relevance of productivity changes to the study question is discussed.	No	Not applicable	No	No	Yes	No
16. Quantities of resources are reported separately from their unit costs.	Yes	Yes	Yes	Yes	Yes	No
17. Methods for the estimation of quantities and unit costs are described.	Yes	Yes	Yes	Yes	Not fully	Yes

Question	Botteman et al 2006	Ross et al 2004 (HTA report)	De Cock 2005a	De Cock 2005b	Hillner et al 2000	Dranitsaris et al 1999
18. Currency and price data are recorded.	No	Yes	No	No	No	Yes
19. Details of currency of price adjustments for inflation or currency conversion are given.	No	Not applicable	Not applicable	Not applicable	No	Yes
20. Details of any model used are given.	Yes	Yes	Not clear	Not clear	Not clear	Yes
21. The choice of model used and key parameters on which it is based are justified.	No	Yes	No	No	No	Yes
22. The horizon of costs and benefits is stated.	Yes	Yes	No	No	Yes	Yes
23. The discount rate is stated.	Yes	Yes	No	No	Yes	Yes
24. The choice of rate is justified.	Yes	Yes	No	No	Not applicable	Not applicable
25. An explanation is given if costs or benefits are not discounted.	NA	NA	No	No	Yes	Yes
26. Details of statistical test and confidence intervals are given for stochastic data.	Yes	No	No	No	No	Not fully
27. The approach to sensitivity analysis is given.	Yes	Yes	Yes	Yes	Not fully	Yes
28. The choice of variables for sensitivity analysis is justified.	No	Yes	Yes	Yes	Yes	No
29. The ranges over which the variables are varied is stated.	Yes	Yes	No	No	No	Yes
30. Relevant alternatives are compared.	Yes	Yes	Yes	Yes	Yes	Yes
31. Incremental analysis is reported.	Yes	Yes	Yes	Yes	Not clear	Yes
32. Major outcomes are reported in a disaggregated as well as aggregated form.	Yes	Yes	Yes	Yes	Yes	Yes
33. The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes	Yes
34. Conclusions followed from the data reported.	Yes	Yes	Yes	Yes	Yes	Yes
35. Conclusions are accompanied by the appropriate caveats.	Yes	Yes	Yes	Yes	Yes	Yes
36. Generalisability issues are addressed.	No	Yes	Yes	Yes	No	No

6.5 Management of brain metastases

Short summary

The papers addressing the management of brain metastases were mainly retrospective case series none of which were of particularly good quality. Most studies did not differentiate between single, multiple or solitary metastases. Two papers specifically addressed the treatment of leptomeningeal metastases (Rudnicka *et al.*, 2007 and Fizazi *et al.*, 1996).

Papers were reviewed on surgery (Pieper *et al.*, 1997 and Wroski *et al.*, 1997) stereotactic radiosurgery (Comb *et al.*, 2004, Lederman *et al.*, 2001, Amendola *et al.*, 2000, Firlík *et al.*, 2000, Levin *et al.*, 2002, Akyurek *et al.*, 2007 and Muacevic *et al.*, 2004) chemotherapy (Rivera *et al.*, 2006, Rosner *et al.*, 1986, Boogerd *et al.*, 1992, Franciosi *et al.*, 1999, Oberhoff *et al.*, 2001, Lassman, 2006 and Trudeau, 2006) and whole brain radiotherapy (WBRT) (Bartsch *et al.*, 2006, Fokstuen *et al.*, 2000, Korzeniowski and Szpytma 1987, Lenztsch *et al.*, 1999, Liu *et al.*, 2006, Ogura *et al.*, 2003 and Mahmoud-Ahmed *et al.*, 2002, Viani *et al.*, 2007 and Johansen *et al.*, 2008).

WBRT of cerebral metastases resulted in median overall survival of between approximately 4 and 7 months. Patients who received whole brain radiotherapy after surgery had improved survival with a median overall survival of approximately 15 to 16 months. However, where measured, performance status did not improve as a result of surgery. Recursive partition analyses of retrospective WBRT data by one group identified prior surgery, absence of extracranial metastases and RPA class I as significant prognostic factors for survival. A much smaller study found only single vs multiple brain metastases of significance.

Treatment with stereotactic radiosurgery (SRS) resulted in median overall survival ranging from 7.5 to 15 months. Of those receiving SRS, patients with smaller tumours seemed to fare better. Most studies predicted better survival for younger patients and those with good performance status. First-line therapy with SRS was comparable in terms of response and survival to salvage therapy after WBRT in one poor quality study.

The studies analysing data on a variety of chemotherapeutic agents reported extremely variable response and survival data and, as patient numbers were low in each study, no one agent or combination of agents appeared to be better than any other in the treatment of brain metastases. Response rates of up to 64% were reported with median overall survival to a maximum of 61 months in one study. The standard of evidence was weak.

Chemotherapy, including high dose intravenous methotrexate in one study, appeared to be crucial in the treatment of leptomeningeal metastases and both intrathecal and intravenous chemotherapy improved patient survival. WBRT may have been shown in other studies to have improved quality of life but had a questionable effect on survival for these patients.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with up to 3 solitary brain metastases	<ul style="list-style-type: none"> • Surgery alone • Surgery and external beam RT • External RT alone 	Each against the other and either with or without rehabilitation	<ul style="list-style-type: none"> • Improved performance status • Symptom control

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with multiple brain metastases	<ul style="list-style-type: none"> • Stereotactic radiotherapy • Steroids • External beam RT • No active treatment • Systemic therapy 		<ul style="list-style-type: none"> • Progression free survival • Overall survival • Quality of life
Patients with meningeal disease	<ul style="list-style-type: none"> • Intrathecal chemotherapy • External beam RT • Systemic therapy • None 		

NB The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

There were 21 papers reviewed for this question and most were retrospective case series. Papers could not be classed depending on type of brain metastasis since, with few exceptions, studies included patients with single and multiple metastases, solitary metastases, widespread disease, recurrence and, occasionally, meningeal carcinomatosis. The majority of papers were from the USA (n = 9) and Europe (n = 9) with the rest from Scandinavia (n = 1) and Asia (n = 2). There were few prospective studies, none of good quality. The total patient number was 1,481.

Surgery

There were two papers (Pieper *et al.*, 1997, Wroski *et al.*, 1997) about the use of surgery for the treatment of brain metastases due to breast cancer – both were retrospective reviews of data from patient case files from a similar chronological period. Pieper *et al.* (1997) reported the changes in performance status and overall survival (OS) of 63 patients who had undergone full or partial resection of brain metastases. All patients had progressive or recurrent brain disease and some (56%) also had extracranial metastases whilst others had single (87%) or multiple lesions (13%) but no other metastatic disease. Following surgery, 62/63 patients received adjuvant therapy consisting of chemotherapy (n = 8) whole brain radiotherapy (WBRT, n = 21) or both (n = 33). Median OS overall = 16 months, median time to recurrence = 15 months with a 5yr survival rate of 17%. Performance status improved in only 11 patients. Patients who received WBRT after surgery had a significantly reduced risk (62%) of mortality.

Wroski *et al.* (1997) similarly reported on 70 patients who had undergone en bloc or piecemeal resection of brain metastases. 77% of patients had single brain metastases, 23% had meningeal disease and 39% of patients had recurrent brain disease. The OS was 15.8 months in those individuals who received WBRT after surgery (n = 47) compared with other patients (n = 15) who had WBRT before surgery and whose median OS was 6.3 months (P < 0.0016). Patients with meningeal carcinomatosis had a reduced OS (5.6 months) compared with those with brain metastases. The median OS for all patients, regardless of condition or treatment regime, was 13.9 months and the 5yr survival rate was 7%.

Death as the result of neurological progression was between 38% (Pieper *et al.*, 1997) and 51% (Wroski *et al.*, 1997). The limited and retrospective data suggest that OS after surgery is

enhanced in patients with good performance status, controlled or absent systemic disease and who receive post-surgical WBRT.

Chemotherapy

There were six papers describing the treatment of brain metastases with chemotherapy. Three studies were retrospective (Fizazi *et al.*, 1996, Rivera *et al.*, 2006 and Rosner *et al.*, 1986) and three were prospective: two case series (Boogerd *et al.*, 1992, Franciosi *et al.*, 1999) and a phase II non-randomised trial (Oberhoff *et al.*, 2001). Unfortunately, papers differed from one another in respect of the specific interventions, with the exception of Boogerd *et al.* (1992) and Rosner *et al.*, (1986) who both recorded the response to a combination of cyclophosphamide, methotrexate and 5'-fluorouracil, albeit at different dosages. The total number of patients reviewed was 294. The main outcomes: median OS, tumour response and response duration are given in Table 1 below. Evidence was weak in favour of any one drug intervention.

Fizazi *et al.* (1996) reviewed data on the treatment with intrathecal high- or low-dose methotrexate for 68 patients with meningeal carcinomatosis and was the only paper to deal with this group exclusively. Subjects were also given other chemotherapy for symptomatic, widespread disease. The higher dose methotrexate appeared to be more effective and resulted in a longer OS but, since this was a review and the patients weren't prospectively randomised, this conclusion may not be reliable. In addition, the contribution of systematic chemotherapy may be a confounding factor since the drug combinations included 5'-fluorouracil and cyclophosphamide which appear to be also prescribed for CNS metastases. Neutropenia may have contributed to the death of 7 patients.

Rivera *et al.* (2006) presented a retrospective review of 24 patients who were given capecitabine and temozolomide for cerebral metastases. Primarily a dose-finding study, nonetheless, survival data were retrieved and reported. The follow-up at this institution appears to have been very thorough and included assessments of neurocognitive function before during and after treatment which, in this study, showed no significant change from baseline. Over 70% of the patients experienced disease progression during the study and the response rate was low overall with only 4 patients having a full or partial response with a median duration of only 8 weeks. The authors did suggest that this regime might be useful for those patients with advanced disease who could not have, or who had refused, WBRT. There were 22 reported grade 3 or 4 adverse events, most commonly haematological.

The third retrospective study, by Rosner *et al.* (1986) reviews data from 100 patients treated for brain metastases with four chemotherapy regimes: Cyclophosphamide, 5'-fluorouracil and prednisone (n = 52), Cyclophosphamide, 5'-fluorouracil, methotrexate, prednisone and vincristine (n = 35), Methotrexate, prednisone and vincristine (n = 7), Cyclophosphamide, prednisone and doxorubicin (n = 6). The sub-group sizes make comparisons between them of poor statistical value but there was no significant difference between treatments in the two largest sub-groups. Those patients with a positive response to chemotherapy were reported to have had a good clinical improvement of symptoms in the CNS and 20 individuals were apparently symptom-free during their remission with a 1 year survival rate of 31%. All but 2 of these patients had established extracranial metastases.

Boogerd *et al.* (1992) described a prospective case series of patients recruited at a single centre in the years between 1987 and 1990. Patients received cyclophosphamide, 5'-fluorouracil and methotrexate (or doxorubicin) for up to 9 four-week cycles. Patients who progressed on this therapy were given WBRT or further chemotherapy. 50% of patients died from neurological causes and the overall neurological response was over 54%. These subjects had all forms of disease i.e. multiple metastases (n = 17), single metastases (n = 5), solitary metastases (n = 6) or more disseminated systemic disease (n = 16) but those with meningeal carcinomatosis were excluded. Again, small sub-group numbers make comparisons statistically unsound. The authors had also compared results with an historical group of selected individuals who had received

WBRT rather than chemotherapy but without evaluation of the demographics the comparison might be of little value.

Franciosi *et al.* (1999) presented a prospective case series of 56 patients, part of a larger study group, who mainly (n = 45) had solitary metastases, either single (n = 20) or multiple. Participants were randomised into two arms and received cisplatin with etoposide at two different dosages. The 'technical randomisation' was to ensure that data would be analysed by the intention-to-treat principle but no methodology was elaborated, nor were there details of how or by whom the tumour response was assessed. Tumour response was 38% and survival at 1yr was 32%. There were three apparently treatment related deaths from gastric bleeding, gastric perforation or neutropenia. This study seems to have been well conducted but was not so well reported.

Oberhoff *et al.* (2001) conducted a phase II study of a small (n = 24) group of breast cancer patients with CNS metastases who were recruited over a 16 month period and were given topotecan chemotherapy in 3-week cycles whilst receiving no other treatment (other than radiotherapy for bone metastases). 5 patients were withdrawn within the study period and 4 of these were for treatment related adverse events. The tumour response was 37.5% with a median duration of about 4 months. There were many (n = 158) grade 3 or 4 adverse events reported in the 93 treatment cycles which were achieved, most of which were haematological. This was a small pilot study which was statistically underpowered and from which it would be difficult to gauge the advantages of this therapy.

Study	No	Metastasis type*	Chemotherapy**	Median OS	Median RD	Response rate %
Boogerd <i>et al.</i> , 1992	22	5 single 17 multiple 4 recurrent 6 solitary 16 systemic	CYC + MET + 5'-FLU	25 weeks (range: 2-83)	30 weeks (range: 15-66)	64 (all)
Fizazi <i>et al.</i> , 1996	68	68 meningeal 2 solitary 66 systemic	Intrathecal MET (HD or LD)	HD = 98 days (95%CI: 53-179) LD = 49 days (95%CI: 32-67)	128 days	41.5 (HD) 14.3 (LD)
Franciosi <i>et al.</i> , 1999	56	20 single 36 multiple 45 solitary 11 systemic	CIS + ETO (2 doses)	all = 31 months (range: 0-287)	all = 33 months (range: 8-93)	38 (all)
Oberhoff <i>et al.</i> , 2001	24	6 solitary 18 systemic	TOP	all = 6.25 months (95%CI: 4.7-9.6)	all = 124 days (range: 35-151)	37.5 (n=16)
Rivera <i>et al.</i> , 2006	24	24 multiple 10 recurrent 24 systemic	CAP + TEM (4 doses)	not reported	all = 8 weeks (range: 6-64)	16.6 (all)
Rosner <i>et al.</i> , 1986	100	2 solitary 98 systemic	<ul style="list-style-type: none"> • CYC + 5'-FLU • CYC + 5'-FLU + MET • MET + VIN • CYC + DOX 	all = 5.5 months	7 months (50 patients who responded)	<ul style="list-style-type: none"> • 52 (n=52) • 54 (n=35) • 43 (n=7) • 17 (n=17)

Table 6.5.1 * single – patient had one CNS metastasis, multiple – patient had more than one CNS metastasis, solitary – patient had no known extracranial metastases, systemic – patient had widespread metastatic disease, meningeal – patient had meningeal carcinomatosis, recurrent – patient had recurrent CNS disease.

** CYC – cyclophosphamide, MET – methotrexate, 5'-FLU - 5'-fluorouracil, CIS – cisplatin, ETO – etoposide, TOP – topotecan, CAP – Capecitabine, TEM – temozolomide, DOX - doxorubicin

Radiotherapy

Six fairly recent papers addressed stereotactic gamma knife radiosurgery or radiotherapy (SR) via linear accelerator in the treatment of brain metastases and all are retrospective case series. The total number of patients was 383. The median OS and response rates, where given, are shown in Table 8.5.2 below.

Combs *et al.* (2004) presented a case series of three groups of patients that had received (a) SR via a linear accelerator with 6-MeV or 15-MeV photons and single doses between 15 Gy to 20 Gy (n = 10) (b) WBRT at doses of between 30 Gy to 40 Gy with a SR boost at a single dose of 10 Gy to 20 Gy (n = 13) or (c) WBRT with SR as salvage therapy for tumour recurrence (n = 39). Patients were grouped by recursive partitioning analysis (RPA) into three classes: Class I: patients with KPS \geq 70, < 65 years of age with controlled primary and no extracranial metastases, Class III: KPS < 70, Class II: all others. Overall survival was not significantly different between these classes but was significantly longer for patients < 40 years (P = 0.04) and for those who had received WBRT with the SR boost (P = 0.036). The majority of patients were in the high risk class RPA II.

Lederman (2001) presented data on 60 patients who had SR via a linear accelerator at a median prescribed dose of 600 cGy (range: 1200 cGy to 2500 cGy). This was delivered as a single dose to patients prior to 1994 and as hypofractions thereafter. The median OS was 7.5 months which is lower than some other studies but the median tumour volume (10.2 ml) may have been a factor since tumour volume < 12ml (P = 0.02) was a positive predictor for enhanced survival and hence this group as a whole may have been disadvantaged. The authors conclude that patients with progression of brain and systemic disease appear to receive good palliation by WBRT with SR boost. They add that the number of brain metastases and the presence of extracranial metastases were not prognostic variables for OS if measured from the time of diagnosis of breast cancer.

Amendola *et al.* (2000) described a series of patients who had been treated with gamma knife SR in single doses between 6 Gy to 25 Gy. An analysis of prognostic factors suggested, unlike most studies, a superior OS outcome for patients over the age of 65 years and a better local control for those patients with a greater number of lesions (percentage of responding lesions). The 1 year survival rate was 40%. All patients had extracranial metastases and the majority had multiple brain lesions. There were only three adverse events reported.

Firlik *et al.* (2000) described the outcomes for 30 patients that had undergone gamma knife SR at doses between 12 Gy to 20 Gy. Local control was achieved for the majority (93%) of patients with a median OS of 13 months. Positive predictors for longer survival were smaller tumour volume (P = 0.05) and single, as opposed to multiple, metastases (P = 0.02). Nearly half the patients had tumour volumes < 1ml. The majority of patients (87%) had already received WBRT for treatment of their brain metastases.

Levin *et al.* (2002) reported on a low number (n = 12) case series of patients that had received gamma knife SR to a median prescribed dose of 17Gy. All patients had previously received HD-chemotherapy with stem cell rescue for brain metastases and achieved a median OS of 11.5 months after SR. The authors felt that SR was preferable to WBRT for patients that had previously received HD-chemotherapy because of the reduced risk of additive neurotoxicity. This was a poor quality study in many respects.

Muacevic *et al.* (2004) reviewed data from 151 patients that received gamma knife SR on an outpatient basis. The mean dose was between 19 Gy and 37 Gy. 9 patients had progressive disease after treatment and 21 patients died from neurological causes. The local response rate was 94% with a median OS of 10 months. The RPA I classification was a prognostic variable ($P < 0.001$) and age > 65 years was a negative predictor of OS. The majority of patients had multiple metastases ($n = 63\%$), extracranial disease ($n = 88\%$) and were classed as RPA II (72%).

Whole brain radiotherapy

Seven papers described studies where the use of whole brain radiotherapy (WBRT) to treat brain metastases was investigated. All are retrospective case series with a total patient number of 671. The median OS and response rates, where given, are shown in Table 2 below.

Bartsch *et al.* (2006) presented a moderate number ($n = 174$) case series of patients who received WBRT with or without an additional boost, depending on the size of the lesion. Prognostic factors for improved OS included receiving systemic therapy after WBRT, receiving intensified local treatment after WBRT, the absence of visceral metastases and good KPS. 26 patients had solitary metastases whilst the remaining patients had bone or soft tissue ($n = 36$) or visceral ($n = 26$) metastases or both. The median OS for the group was 7 months.

Fokstuen *et al.* (2000) reported survival data from a retrospective series of 99 patients treated with WBRT alone. 8 patients had leptomeningeal carcinomatosis whilst 91 patients had cerebral metastases. Using patients with solitary metastases as a reference point the authors determined that patients with non-visceral metastases had a similar OS but patients with visceral metastases had a significantly poorer OS. The median OS for the entire group was 5 months.

Korzeniowski *et al.* (1987) described survival outcomes for 36 patients who had received WBRT and who were followed up for a minimum of 3 years. The median OS for the group was 4.6 months and many (66%) patients had remission of their symptoms but for a mean period of less than 3 months. The OS of this group was superior to patients that did not show this level of response.

Lenzsch *et al.* (1999) retrieved data on 162 patients who had received different interventions for brain metastases, but the majority of whom were given WBRT. Sub group analyses included all patients regardless of intervention and determined significant prognostic factors for OS which included the number of metastases, grade of the breast cancer, radiation dose and patient performance status. This was a very thorough analysis but there may be selection bias in the subjects chosen and some of the sub-groups were small. The authors concluded that patients with solitary metastases had better survival outcomes than those with extracranial disease.

Liu *et al.* (2006) described a series of 48 patients who had been treated with WBRT in a variety of dosages and fraction schedules. The OS for the group was over 7 months and the 1 year survival rate was 37%. Independent prognostic factors for OS were high performance status, having a single metastasis, being RPA I and being under the age of 50 years. In multivariate analysis only performance status and the number of metastases were significant.

Mahmoud-Ahmed *et al.* (2002) detailed 112 patients who had received WBRT, mainly by the standard technique, for brain metastases. The main reported outcome was OS which was analysed by sub-group to determine prognostic factors. These were found to be high performance status, RPA class I and radiation dose. Multivariate analysis only identified higher performance status as a factor for enhanced OS. The OS for the entire group was just over 4 months.

Study	n =	Metastasis	Intervention	Median OS	Response rate %
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		type*			
Amendola <i>et al.</i> , 2000	68	15 single 53 multiple 68 systemic	SR	7.8 months	response by lesion: 1 lesion = 73% 1-3 lesions = 83% 4-7 lesions = 91% >8 lesions = 96%
Combs <i>et al.</i> , 2004	62	14 single 48 multiple 29 solitary 33 systemic	SR (n=10) WBRT with SR boost (n=13) WBRT with SR salvage (n=39)	15 months (range: 1-276)	not reported
Firlik <i>et al.</i> , 2000	30	14 single 16 multiple 15 solitary 15 systemic	SR	13 months (95%CI: 9-17)	93%
Lederman <i>et al.</i> , 2001	60	19 single 41 multiple 26 solitary 34 systemic	SR	7.5 months (95%CI: 4.6-10)	not reported
Levin <i>et al.</i> , 2002	12	not reported	SR	11.5 months (range: 1-32)	not reported
Muacevic <i>et al.</i> , 2004	151	56 single 95 multiple 18 solitary? 133 systemic	SR	10 months	94%
Bartsch <i>et al.</i> , 2006	174	26 solitary 148 systemic	WBRT or WBRT with SR boost	7 months (95%CI: 5.1-8.9)	not reported
Fokstuen <i>et al.</i> , 2000	99	25 solitary 74 systemic 8 meningeal	WBRT	5 months (range: 1-90) OS after diagnosis	45% improvement of symptoms
Korzeniowski <i>et al.</i> , 1987	36	8 solitary	WBRT	4.6 months	66% improvement of symptoms
Lentzsch <i>et al.</i> , 1999	162	49 single 113 multiple 27 solitary 135 systemic	WBRT surgery + WBRT chemotherapy (for MBC)	~6 months (range:1 wk-10yrs)	not reported
Liu <i>et al.</i> , 2006	48	21 single 27 multiple 13 solitary 35 systemic	WBRT	7.3 months	56% improvement of symptoms
Mahmoud- Ahmed <i>et al.</i> , 2002	116	20 single 96 multiple 37 solitary 79 systemic	WBRT with boost (n=7)	4.2 months	not reported

Ogura <i>et al.</i> , 2003	36	4 single 32 multiple 10 solitary 26 systemic	WBRT with boost (n=10)	7.9 months	81% after 1 month
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Table 6.5.2 *single metastasis – patient had one CNS metastasis, multiple – patient had more than one CNS metastasis, solitary – patient had no known extracranial metastases, systemic – patient had widespread metastatic disease, meningeal – patient had meningeal carcinomatosis

Ogura *et al.* (2003) presented a small case series of 36 patients who received WBRT, the dosage and fractionation being determined by the projected life expectancy of each individual. Prognostic factors were shown to be age (cut-off at 53 years), bone as opposed to other extracranial metastases (the majority of the patients had systemic disease and multiple brain metastases). Unlike other studies, patients of higher performance status were not found to have an advantage over others in terms of OS but this might be due to the classification system (WHO rather than KPS) being used. Median OS for the entire group was 7.9 months.

The papers discussing radiotherapy were of variable quality. However, all patients had breast cancer and all forms of brain metastases i.e. single, multiple, solitary such as might be seen in practice. Stereotactic radiotherapy seems to have been more successful for patients of a younger age, with lower tumour volume or for those who have received the SR as a boost to standard WBRT. In terms of survival WBRT was advantageous to patients of younger age, having a low number of brain metastases, a lack of visceral metastases and in particular a high performance status. Not surprisingly, it therefore seems that radiotherapy is more efficient at prolonging life in those patients who already have a better prognosis.

The median OS for all forms of RT treatment is between 4 and 15 months and there is no clear indication why some studies vary so much from others but this may be due to selection bias on the part of the individuals who selected the cases to review, the different treatment regimes, doses or fractionation schedules or to the numbers of patients having any particular type of metastatic disease. Very few authors presented data with confidence intervals so it is not possible to state whether the variability in OS is statistically significant between studies.

References

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Evidence tables

Question: Patients with solitary, single or multiple brain or leptomeningeal metastases
Created by: Karen Francis on 03/05/2007

Boogerd <i>et al.</i> (1992)
Design: Prospective case series (prognosis), evidence level: 3 Country: Netherlands, the
Inclusion criteria: Patients with breast cancer and unresectable or recurrent brain metastases
Exclusion criteria: Clouded consciousness persisting after corticosteroid therapy Hemiplegia persisting after corticosteroid therapy Meningeal carcinomatosis Serious myelosuppression Short life expectancy (not defined) Second primary tumour
Population: Number of patients = 22, age range 33 to 72 years, mean age = 49 years
Interventions: CMF (n = 20): Cyclophosphamide at 100 mg per m ² orally on days 1 to 14 + methotrexate at 40 mg per m ² i.v. on days 1 and 8 + 5'-fluorouracil at 600 mg per ml i.v. on days 1 and 8 in 4 week cycles for 6 cycles (or 9 cycles depending on response). CAF (n = 2): Cyclophosphamide at 500 mg per m ² i.v. + doxorubicin at 50 mg per m ² i.v. + 5'-fluorouracil at 500 mg per ml i.v. once every 3 weeks. Dose modifications were put in place if patients experienced grade 2 haematological toxicity. 20/22 patients received dexamethasone, the dosage of which was tapered depending on the neurological response to therapy. For stable disease or progression of brain disease WBRT replaced chemotherapy unless previously irradiated in which case chemotherapy was repeated.
Outcomes: Tumour response: Complete response (CR), Partial response (PR), Minimal response (MR), Stable disease (SD), Disease progression (PD), No evidence of disease (ND), Not evaluable (NE). Overall survival (OS) measured from the day of the diagnostic scan. Response duration (RD).
Follow up: Brain metastases were originally diagnosed by CT scan. Patients underwent neurological examination and assessment of systemic disease every three weeks or earlier in the case of disease progression. Tumour response was evaluated at week 2, 6 and 9 or at clinical progression.

4/22 patients were not examined at 3 weeks due to death from pulmonary embolism, intracranial haemorrhage or gastric perforation.

11 patients died from neurological disease, 3 from systemic disease, 3 from intercurrent disease and 5 patients were still alive at the end of the study.

Results:

Neurological response (n = 18):

Systemic disease:

CR = 1

PR = 2

SD = 10

ND = 3

NE = 5

PD = 1

CNS response:

CR = 2

PR = 10

MR = 1

SD = 1

NE = 6

PD = 2

Median RD: chemotherapy (n = 22) = 30 weeks (range: 15-66)

Median RD: RT (n = 29) = 10 weeks (range: 8-91)

Median OS: chemotherapy = 25 weeks (range: 2-83)

Median OS: RT = 10 weeks (range: 1-107)

Median OS of patients responding to chemotherapy = 66 weeks (range: 22-83)

Median OS of patients responding to RT = 26 weeks (range: 18-107)

Median OS: solitary metastases (n = 6) = 26 weeks

Median OS: single metastasis (n = 5) = 9 weeks

Grade 3 or 4 adverse events:

Haematological toxicity = 4

6/7 patients responded to chemotherapy despite relapsing previously on the same regime.

General comments:

This paper describes a comparison between a prospective series of patients with brain metastases from breast cancer who received chemotherapy and a historical control group which had received WBRT. The groups did not appear to be well matched in some respects and there was no statistical analyses offered. Hence, although data are included for both groups, comparisons between them should be viewed with great caution.

Patients were recruited from September 1987 and the study was closed in September 1990. 17/22 patients had multiple metastases and 5/22 patients had a single lesion. 4/5 single lesions were inoperable recurrences of previously resected or irradiated metastases. 6/22 patients had only CNS metastases and the remaining 16 patients had more disseminated disease, although only 10 of these had progressive disease at the time of the study.

Franciosi <i>et al.</i> (1999)
Design: Prospective case series (prognosis), evidence level: 3 Country: Italy
Inclusion criteria: Brain metastases not amenable to surgery or previously treated with RT. Diagnosis of brain metastases measurable or evaluable by CT Normal bone marrow Normal renal function No additional tumours Lack of severe cardiac disease No prior treatment with cisplatin and etoposide No prior treatment with chemotherapy after diagnosis of brain metastases No prior RT to the brain Oral informed consent.
Exclusion criteria: Patients with extracranial visceral disease >2 brain lesions Metastases in inoperable cerebral sites Refusal of surgery
Population: Number of patients = 56, age range 41 to 75 years, median age = 56 years
Interventions: Arm A: Cisplatin (P) at 100 mg per m ² i.v. on day 1 with hydration and mannitol forced diuresis. Etoposide (E) at 100 mg per m ² i.v. on days 1, 3 and 5 every 3 weeks Arm B: Cisplatin (P) at 100 mg per m ² i.v. on day 1 with hydration and mannitol forced diuresis. Etoposide (E) at 100 mg per m ² i.v. on days 4, 6 and 8 every 3 weeks. Treatment was postponed for atypical white blood cell or platelet levels (defined). Nephrotoxicity was monitored by testing for creatinine clearance rates on day 18 of each course and treatment was postponed accordingly if levels fell > 25%. If any toxicity failed to resolve after 4 weeks treatment was withdrawn permanently. Patients received a maximum of 6 cycles of therapy.
Outcomes: Tumour response: complete response (CR), partial response (PR), no change (NC) or disease progression (PD), Time to progression (TTP), Time to treatment failure (TTF), Response duration (RD), Overall survival (OS). Adverse events.
Follow up: Patients were initially staged including clinical examination, chest X-ray, bone scan, liver ultrasound (or X-ray), complete blood count and biochemical testing. Baseline evaluation of the brain was by CT scan, repeated after the second course of chemotherapy and every course thereafter. Patients received a CT scan and clinical examination before each treatment cycle to assess toxicity, tumour response and oedema.
Results: Median number of treatment cycles = 3 (range: 1-8)

Tumour response:

CR = 7 (13%)

PR = 14 (25%)

ORR (CR + PR) = 21 (38%)

PD = 15

NC = 12

No response = 8 - these patients either had insufficient treatment or their responses were not evaluated.

11 patients with a positive CNS tumour response also had evaluable extracerebral metastases - the response in these areas was :

CR = 3

PR = 3

NC = 3

PD = 1

Median TTP (n = 56) = 17 months (range: 0-287+)

Median RD (n=21) = 33 months (range: 8-93)

Median OS (n=56) = 31 months (range: 0-287)

Survival at 1 year = 32%

Survival at 2 years = 9%

Survival at 3 years = 3%

Adverse events:

3 patients died: 1 from gastric bleeding, 1 of gastric perforation with peritonitis and 1 from neutropenic fever and diarrhoea. 3 patients were suspended from treatment due to atrial fibrillation, tubular kidney damage or febrile neutropenia with pneumonitis.

General comments:

This paper describes a larger prospective study of the use of cisplatin and etoposide in patients with brain metastases. 56/116 patients had breast cancer and were separately reported from others with lung cancer or melanoma. Patients were treated between December 1986 and July 1993 at several Italian centres.

11/56 patients had extracranial metastases and 45 had a solitary metastasis. 20/56 had a single lesion, 14/56 patients had 2 lesions and 22/56 patients had more than 2 lesions.

The randomisation into 2 treatment groups was with the aim of forcing investigators at the various hospitals to report to the randomisation centre such that patients would be seen on an intention-to-treat basis before commencement ("technical randomisation"). Hence the data were analysed together.

No statistical methods are detailed. Data are presented as point estimates and ranges.

There are no details of how tumour response was evaluated or whether or not such evaluation was conducted by independent reviewers. It is apparent from the text that many patients received corticosteroids, the contribution of which cannot be discounted from the observed response to chemotherapy.

Amendola *et al.* (2000)

Design: Retrospective case series (prognosis), evidence level: 3

<p>Country: United States</p>
<p>Inclusion criteria: Failure of WBRT and surgery with disease progression OR Elective SR for newly diagnosed brain metastases</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 68, age range 25 to 80 years, median age = 52 years</p>
<p>Interventions: Gamma knife SR. Performed by Leksell gamma unit. Single doses of between 6 Gy and 25 Gy to the 35% to 85% isodose line with 95% of the minimum doses between 15 Gy and 24 Gy.</p>
<p>Outcomes: Local control, Overall survival (OS), Adverse events</p>
<p>Follow up: Baseline assessment included MRI which was repeated 4 weeks after SR and every 3 months thereafter.</p> <p>Median follow-up per patient was 7.8 months (range: 0.2-42.8).</p> <p>At the end of the study 51 patients had died of causes unrelated to brain metastases. However, only 56 patients had the cause of death documented.</p>
<p>Results: Mean volume of all lesions = 3.3 ml</p> <p>Local control (% of lesions) Patients with a single lesion (n = 15) = 73% Patients with 1-3 lesions (n = 26) = 83% Patients with 4-7 lesions (n = 18) = 91% Patients with >8 lesions (n = 24) = 96%</p> <p>Rate of patient survival at 1 year = 27/68 (40%) Rate of patient survival at 2 years = 9/68 (13%) Rate of patient survival at > 3 years = 2/68 (3%)</p> <p>Median OS for all patients = 7.8 months Median OS for patients < 65 years = 7.7 months Median OS for patients > 65 years = 13.4 months</p> <p>Tumour control for patients with 1-3 lesions (n = 26): 34/41 lesions were treated once 6/41 lesions were treated twice 1/41 lesions were treated four times Local control by lesion = 83%</p> <p>15 patients required treatment for a single metastasis. 11/15 of these patients achieved local tumour control.</p> <p>Tumour control for patients with 4-7 lesions (n = 18): 83/92 lesions were treated once 8/92 lesions were treated twice 1/92 lesions were partially retreated</p>

Local control rate by lesion = 90%

Tumour control for patients with > 8 lesions (n = 24):

368/385 lesions were treated once

17/385 lesions were treated twice

Local control rate by lesion = 96%

For local control (but not overall survival) the number of lesions was significant (P = 0.0001)

Adverse events:

3/68 patients developed necrosis in the brain after SR.

General comments:

This paper describes a retrospective review of two groups of patients that had received gamma knife SR. One group (n = 38) had been previously treated with WBRT (and 2 even with SR) such that SR was given following progression. The other group (n = 30) were patients that had not received WBRT prior to SR.

66/68 patients had their primary cancer controlled but 2 had chest wall recurrence. All patients had extracranial metastatic disease.

15/68 patients had a single lesion

26/68 patients had 1-3 lesions

18/68 patients had 4-7 lesions

24 patients had ≥ 8 lesions

Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups.

Authors conclude that SR is a safer method for local tumour control and, in comparison to conventional RT, avoids the possibility of death due to neurological progression in the majority (91%) of patients.

Bartsch *et al.* (2006)

Design: Retrospective case series (prognosis), evidence level: 3

Country: Austria

Inclusion criteria:

None stated

Exclusion criteria:

None stated

Population:

Number of patients = 174, age range 27 to 81 years, median age = 55 years

Interventions:

Whole brain irradiation (WBRT) using a 6MV linear accelerator. The total dose was 30 Gy applied in 10 fractions over two weeks.

For lesions < 2 cm an additional SR boost was applied with a dose of 16 Gy to 20 Gy at the 50% isodose. Alternatively such patients were given WBRT boost with 20 Gy applied at 80% isodose.

For lesions > 2 cm patients were given WBRT boost with x2 10 Gy.

Outcomes:

Time to progression (TTP) was measured from time of onset of treatment until time of progression, Overall survival (OS) was the time from onset of treatment until death.

Follow up:

CT or MRI scans were performed one and three months after WBRT and every three months thereafter.

TTP data was available for 150/174 patients and all patients were evaluable for the analysis of overall survival.

Results:

Median TTP for all patients = 6 months (95%CI: 4.7-7.4)

Median OS for all patients = 7 months (95%CI: 5.1-8.9)

Median OS for patients receiving systemic therapy after WBRT = 10 months (95%CI: 8.1-11.9)

Median OS for patients not receiving systemic therapy after WBRT = 5 months (95%CI: 3.9-6.1)

P = 0.002

Median OS for patients receiving intensified local treatment (boost irradiation or surgical resection) = 10 months (95%CI: 8.2-11.8)

Median OS for patients receiving palliative WBRT = 4 months (95%CI: 3.1-4.9) P < 0.001

Median OS for patients with visceral metastases = 5 months (95%CI: 3.4-6.6)

Median OS for patients without visceral metastases = 9 months (95%CI: 4.6-13.4) P = 0.039

Intensified local treatment (P<0.001), palliative systemic treatment (P = 0.001) and KPS (P = 0.002) influenced TTP according to multivariate analysis.

Intensified local treatment (P < 0.004), palliative systemic treatment (P = 0.001) and KPS (P = 0.006) and metastatic sites (P = 0.008) influenced OS according to multivariate analysis.

Univariate analysis showed that boost irradiation had an influence on OS (P = 0.027)

General comments:

This retrospective case series examines data from 174 patients treated with WBRT for brain metastases due to breast cancer at a single centre between 1994 and 2004.

Some patients had received surgery for brain metastases prior to RT dependent on the number of lesions (1-3) and KPS. Treatment decisions were made independent of metastatic disease considerations.

At the time of diagnosis of brain metastases, 26/174 patients had visceral metastases, 36/174 patients had bone or soft tissue metastases and 82 patients had both. The remaining patients (n = 26) had no extracranial metastases.

54/174 patients received boost irradiation after WBRT with a median number of boosted sites = 2.

24/174 received trastuzumab before WBRT and 16 of these resumed treatment after WBRT.

59/174 patients received other systemic palliative treatment.

Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups and the association between survival and various prognostic factors.

Authors report that TTP was not affected (statistically) by age or the number of metastatic sites. Similarly, age did not impact on OS. They conclude that their most important finding was that

patients derived great benefit from systemic treatment or intensive local therapy after WBRT, extending OS and TTP (cerebral) significantly when compared with WBRT alone.

Combs <i>et al.</i> (2004)
Design: Retrospective case series (prognosis), evidence level: 3 Country: Germany
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 62
Interventions: Group I (n = 10): SR. Performed by linear accelerator with 6-MeV or 15-MeV photons. Single doses of between 15 Gy and 20 Gy dependent on tumour size and location Group II (n = 13): WBRT at doses of between 30 Gy and 40 Gy within 3-4 weeks using conventional fractionation. SR was given as a focal boost within 6 weeks of WBRT and delivered as a single dose of between 10 Gy and 18 Gy. Group III (n = 39): WBRT with SR as salvage therapy given for recurrence of brain metastases at a dose of 10 Gy to 20 Gy prescribed to the 80% isodose.
Outcomes: Progression-free interval (PFI), Overall survival (OS), measured from SR to death or end of follow-up, Total survival, measured from first diagnosis of breast cancer to death or end of follow-up.
Follow up: Median follow-up after SR = 11.5 months Follow-up visits occurred 6 weeks after treatment and every 3 months thereafter. At these appointments MRI scans were performed and a thorough neurological examination given. 50/62 patients died by the end of follow-up. 48/50 deaths were due to tumour progression and 2 deaths occurred because of pulmonary embolism or pneumonia.
Results: Median OS after SR = 15 months (range: 1-276) Median time from primary diagnosis to brain metastases = 47 months (range: 0-216) Median total survival = 64 months (range: 14-408) Median total OS: RPA I = 72 months (range: 22-264) Median total OS: RPA II: 64 months (range: 14-408) Median total OS: RPA III: 48 months (range: 27-72) nsd Median OS from SR: RPA I = 9 months Median OS from SR: RPA II = 6 months Median OS from SR: RPA III = 19 months Patients < 40 years had significantly longer OS compared to patients > 40 years (P = 0.04). The number of cerebral metastases did not significantly affect OS.

Patients treated with SR only (group I) showed a significant increase in OS compared with patients given WBRT with SR boost (group II) (P = 0.036).

Median time to local tumour control:

Group I = 6.5 months

Group II = 4 months

Group III = 9 months. nsd between groups I and II

Median time to locoregional tumour control:

Group I = 6.5 months

Group II = 4 months

Group III = 7 months. nsd between groups I and II

General comments:

This paper describes a retrospective study of three groups of patients: one group received SR only, the second received WBRT with SR as a boost and the third group received WBRT with SR as salvage therapy. Patients were treated between January 1986 and January 2003.

14 patients had a single brain lesion. 13 patients had 2-3 brain lesions and 35 patients had ≥ 4 lesions.

14/62 patients had received a surgical resection of a cerebral metastasis prior to RT but none after.

Intermediate risk (RPA I) patients = 34%

High risk (RPA II) patients = 61%

Very high risk (RPA III) patients = 5%

33/62 patients had extracerebral metastases and 29/62 had solitary metastases.

Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups and the association between survival and various prognostic factors.

The authors suggest that WBRT might be omitted in patients with 1-3 brain metastases and progressive cranial disease (i.e. RPA class II). This would mean that chemotherapy (i.e. for advanced breast cancer) might not be delayed as is the case if the patient is receiving WBRT.

The patient numbers in this retrospective review are too low to allow for effective sub-group analyses, particularly with regard to the tumour control between groups I and II which appears to be of no significance. The efficacy of one treatment against another would obviously be better answered by a RCT.

Firlik *et al.* (2000)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States

Inclusion criteria:

Brain metastases from breast cancer.

Previous treatment for brain metastases i.e. WBRT, chemotherapy or 'conventional surgery' was acceptable

Imaging typical for brain metastases

KPS > 50

Tumour diameter < 3 cm

Exclusion criteria: None stated
Population: Number of patients = 30, age range 39 to 70 years, mean age = 55 years
Interventions: Stereotactic radiosurgery (SR) was performed with a cobalt-60 gamma knife using enhanced CT or MRI scans for positioning. The maximum number of lesions treated in a single session was six. SR doses to the tumour margin varied between 12 Gy to 20 Gy.
Outcomes: Tumour control. Overall survival (OS).
Follow up: Mean clinical follow-up was 13 months (median 9 months range: 1-47). All patients had at least 1 documented follow-up. 1 patient was lost to follow-up. At the time of the report, 20 patients had died of progressive systemic disease (n = 8), progression of treated brain tumour (n = 3), development of new brain tumour (n = 1) or both (n = 1). The cause of death was not known for 7 patients. Mean imaging follow-up was 9 months (range: 1-31) using either CT or MRI.
Results: 28 patients had one SR session 2 patients had 2 SR sessions 1 patient had 3 SR sessions Local tumour control rate = 93% Median OS after surgery = 13 months (95%CI: 9-17) Median OS from diagnosis = 18 months (no CI) Positive prognostic variables in univariate analysis were single (as opposed to multiple) metastasis (P = 0.02) and a smaller tumour volume (P = 0.05). Multivariate analysis revealed only the former as a positive predictor of longer survival after SR (P=0.01).
General comments: This paper describes a retrospective review of data from patients that had received SR between May 1990 and July 1997 at a single institute. Information was supplemented by telephone calls to the patient, patient's family or physician. 14 patients had 'solitary' (single) metastases and 16 had multiple metastases. 15 patients had active systemic disease and 15 did not (solitary metastases). 26 patients had received WBRT prior to SR and 5 patients received WBRT after SR. Note that this patient group were selected for lesion size. Of the 58 lesions treated, 27 (46.5%) were < 1ml in volume. Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups and the association between survival and various prognostic factors.

Fizazi <i>et al.</i> (1996)
Design: Retrospective case series (prognosis), evidence level: 3 Country: France
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 68, age range 22 to 77 years, mean age = 52 years
Interventions: HD-MTX: Methotrexate via an intrathecal route at 15 mg once a day for 5 days followed by 9 days rest + hydrocortisone given intrathecally on day 1 of the 14-day cycle. Folinic acid was also given after MTX (n = 41) LD-MTX: Methotrexate via an intrathecal route at 15 mg once a week + hydrocortisone at 125 mg (n = 21) MTX was given until disease progression, relapse or whilst the patient's condition permitted. 6 patients did not receive MTX and 4 of these were given WBRT with thiotepa Patients received chemotherapy for symptomatic systemic disease: Fucontin: 5'-fluorouracil + cyclophosphamide + vindesine Fulon: 5'-fluorouracil + cyclophosphamide + adriamycin Patients with symptomatic meningeal masses also received cranial, craniospinal or spinal RT.
Outcomes: Clinical response. Overall survival (OS) measured from the date of the first intrathecal drug administration to the date of death or last known date alive.
Follow up: Extent of disease was assessed by CT (up to 1989) or MRI (after 1989). Malignant cells were identified by means of lumbar puncture in 90% of patients and by increased CSF protein associated with CT results in the remaining patients. Assessment included neurological examination 2 times a month including a CSF sampling. At the end of the study 60 patients had died as a result of meningeal carcinomatosis (63%), systemic disease (45%) or other causes including infection (22%).
Results: Clinical response - survival of HD-MTX group (n = 41): Positive response = 17 Stabilisation = 14 Progression = 10 Clinical response - survival of LD-MTX group (n = 21): Positive response = 3 (P = 0.03) Stabilisation = 10 Progression = 8 Mean time to clinical response = 30 days (range: 2-68)

<p>Mean duration of response = 128 days</p> <p>Cytological response - HD-MTX: Positive response = 15 (10 of these patients had a +ve clinical response, 4 had stable disease and 1 patients had disease progression)</p> <p>Median OS for all patients = 67 days Median OS: HD-MTX = 98 days (95%CI: 53-179) Median OS: LD-MTX = 49 days (95%CI: 32-67) (P = 0.01 by Wilcoxon test but nsd by Mantel-Cox test)</p> <p>Positive prognostic factors for overall survival: Controlled systemic disease prior to diagnosis (P < 0.05) Initial CSF protein level < 5 g per l (P < 0.05) Concomitant chemotherapy (P < 0.02)</p> <p>Adverse events: Neutropenia - also the main cause of death in 7 patients Mucositis</p>
<p>General comments: This paper describes a retrospective study of 68 patients with breast cancer treated for meningeal carcinomatosis at a single institute between 1979 and 1994.</p> <p>2/68 patients had no evidence of other metastatic disease. 30/68 patients had progressive systemic disease and 34/68 patients had responsive and stable disease.</p> <p>92% of patients had received chemotherapy for metastatic disease and all patients had received chemotherapy for neoadjuvant or adjuvant treatment.</p> <p>Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups.</p> <p>Authors conclude that survival was improved for patients treated with HD- rather than LD-MTX. However, since patients weren't randomised to the two treatment groups this conclusion is not necessarily sound.</p>

Fokstuen <i>et al.</i> (2000)
Design: Retrospective case series (prognosis), evidence level: 3 Country: Sweden
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 99
Interventions: WBRT (n = 91): Radiation was delivered in 2 parallel opposed fields with cobalt 60 in 2-3 Gy fractions to a median dose of 30 Gy (range: 6-60).
Outcomes:

Overall survival (OS) measured after diagnosis of CNS metastases to death or end of study, Improvement of symptoms.
Follow up: There are no details of follow-up.
Results: Median OS after diagnosis of CNS metastases = 5 months (range: 1-90) Using patients with single metastases (n = 25) as a reference, patients with visceral metastases (n = 51) had a significantly shorter survival time (P = 0.001) whilst patients with non-visceral metastases (n = 23) were not significantly different from the reference point. 10 patients with solitary lesions had craniotomy before WBRT. Their median OS = 21 months. Effect of corticosteroids and WBRT on symptoms: Improvement of symptoms = 45% Stability of symptoms = 39% Deterioration of symptoms = 15% Survival was not correlated with WBRT total dose
General comments: This paper describes a retrospective study of 91 patients with breast cancer and cerebral metastases who received WBRT (n = 81) or surgery plus WBRT (n = 10). In addition, 8 patients had breast cancer and leptomeningeal carcinomatosis. Treatment was given between 1979 and 1990 at a single centre. Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups and the association between survival and various prognostic factors. There are little data of evidential value although a lot of information about symptoms and patient demographics (other than age) etc.

Korzeniowski <i>et al.</i> (1987)
Design: Retrospective case series (prognosis), evidence level: 3 Country: Poland
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 36, age range 32 to 70 years, mean age = 47 years
Interventions: WBRT was given using two parallel fields on a cobalt 60 unit. The tumour dose was 20 Gy in 5 fractions for 30 patients and 16 Gy to 20 Gy in 4-6 fractions for 6 patients. 4 patients received a second course of WBRT between 6 weeks to 5 months after their first course. All patients received steroid therapy according to individual requirements.

<p>Outcomes: Overall survival (OS)</p>
<p>Follow up: Minimum follow-up was 3 years.</p> <p>Extent of disease was initially determined in most patients by neurological examination and EEG (CAT scanning being unavailable in this institution at the time of the study). In 11 patients diagnosis of brain metastases was confirmed by other means including arteriography and craniotomy.</p>
<p>Results: Median OS for patients receiving WBRT (n = 36) = 4.6 months Survival at 1 year = 11%</p> <p>Partial remission of neurological symptoms = 24 (66%). Mean time of this remission was 2.8 months. Median OS for these patients = 6 months.</p> <p>No benefit from WBRT = 12 (33%). 3 patients from this group died within 10 days of treatment. Median OS not given in the text but from the graph appears to have been ~1.5 months.</p>
<p>General comments: This paper describes a retrospective case series of women with breast cancer and brain metastases, 36 of whom were treated with WBRT at a single institution from January 1970 and December 1981.</p> <p>Of the 36 patients, 8 had brain metastases only, 4 had also locally recurrent breast cancer and 24 had distant metastases.</p> <p>This is an outdated paper which provides very little in the way of useful evidence. Data are given as point estimates and the patient number is low for the purposes of comparative survival analyses.</p> <p>The authors conclude that in two thirds of their patients, a positive response to WBRT, with remission of neurological symptoms, prolonged overall survival.</p>

Lederman <i>et al.</i> (2001)
<p>Design: Retrospective case series (prognosis), evidence level: 3 Country: United States</p>
<p>Inclusion criteria: Good neurological status (most patients, but not all, had KPS >=70) Primary tumour controlled or absent Other metastases acceptable Single or multiple (up to 16) metastases</p>
<p>Exclusion criteria: None stated</p>
<p>Population: Number of patients = 60, age range 32 to 89 years, median age = 52 years</p>
<p>Interventions: Stereotactic radiotherapy using a median prescribed dose of 600 cGy (range: 400-2500) delivered by Varian 2100-C linear accelerator.</p> <p>Treatment varied around 1994. Prior to this date, patients received a single fraction dose of</p>

1200-2500 cGy but thereafter hypofractionation was used and patients received 2, 3 or 4 fractions - most commonly 2400 cGy in 4 fractions (n = 43).

56/60 patients received WBRT, 54 before SR and 2 after radiotherapy. 58/60 patients had undergone resection of the primary tumour before SR.

Outcomes:

Overall survival (OS) and actuarial survival

Follow up:

Baseline evaluation of brain metastases by contrast MRI. Follow-up scans 6 weeks after radiotherapy and every 3 months for 2 years then every 6 months thereafter. Scans were assessed by independent neuroradiologists.

3 patients failed to complete SR and died within 30 days. 5 patients died within 3 months of SR. 25 patients survived > 6 months.

Results:

Median total volume of all (n = 246) lesions in the 60 patients was 10.2cc

Results for entire cohort (n = 60):

Median OS after SR = 7.5 months (95%CI: 4.6-10)

Median OS from diagnosis of primary = 67.2 months (95%CI: 56.5-80)

Median OS from diagnosis of brain metastases = 15.7 months (95%CI: 12.8-18.8)

Median OS for patients with tumour volume < 12cc (n = 32) = 10 months (95%CI: 7.5-12)

Median OS for patients with tumour volume > 12cc (n = 28) = 4.4 months (95%CI: 1.9-6.5 months) P = 0.02

Results for patients on 4-fraction technique (n = 43):

Median OS for patients with 1-2 metastases (n = 15) = 11.5 months (95%CI: 8.0-13.4)

Median OS for patients with > 2 metastases (n = 28) = 5.6 months (95%CI: 4.6-8.8)

Median OS for patients without other metastases (n = 17) = 8.0 months

Median OS for patients with other metastases (n = 26) = 6.2 months (P = 0.11)

Actuarial survival at 6 months = 54.1%

Actuarial survival at 1 year = 24.6%

Actuarial survival at 2 years = 14.8%

23 patients had disease progression following WBRT and before SR. This group had a median tumour volume of 11.6cc and a median OS of 6.5 months after SR. 5 patients had relapsed after craniotomy and WBRT and had a median OS of 7.5 months after SR. 15 patients were treated de novo and had a median OS of 11.5 months after SR.

Adverse events:

2 patients suffered from radiation necrosis and underwent resection of the affected area.

General comments:

This paper describes a retrospective review of case notes of 60 patients with brain metastases from breast cancer who had received SR between June 1991 and June 1999 in a single treatment centre. The patient group includes women with recurrent disease, solitary metastasis and single or multiple metastases as part of more disseminated disease.

Actuarial survival was performed using Kaplan Meier analysis and comparisons between sub-groups were analysed by the log-rank test. Tests for statistical significance were not reported due to the low patient numbers in each sub-group.

34/60 patients had other distant metastases at the time of diagnosis. 19/60 patients had a single brain metastasis and others had 2 (n = 8), (n = 8), 4 (n = 8), 5 (n = 2) or more (n = 15) brain metastases. Brain metastases were cerebral (n = 35), cerebellar (n = 5) or both (n = 20).

Authors identify three patient groups within their study cohort. Patients with large tumour volumes, symptoms and intracranial pressure tended to succumb regardless of treatment and rarely survived beyond 4 months. Patients with progression of both brain and systemic disease were palliated by radiotherapy and a third group of patients, who responded to treatment, derived a long remission with the ability to receive future re-treatment.

Authors concluded that there was no significant difference in outcome in patients with single brain metastasis compared with patients having two or three metastases. Additionally, the presence of extra-cranial metastases did not appear to affect OS measured from the time of primary diagnosis or following SR, although a significant difference was seen if measured from the time of diagnosis of brain metastasis.

Lentzsch *et al.* (1999)

Design: Retrospective case series (prognosis), evidence level: 3

Country: Germany

Inclusion criteria:

Symptomatic prior to diagnosis

Exclusion criteria:

Isolated leptomeningeal disease

Second neoplastic disease

Population:

Number of patients = 162, age range 30 to 78 years, median age = 50 years

Interventions:

WBRT (n = 145):

Irradiation (60 cobalt of 6MV) with opposing fields with a total dose of 20 to 50 Gy delivered in fractions of 1.5- 3 Gy per day over 2-4 weeks according to the individual. There were no boost doses given.

Surgery (n = 10):

Patients with solitary or a few resectable lesions underwent surgical resection. These patients were given WBRT immediately after surgery or, in the case of relapse, after a second operation.

Adjuvant chemotherapy (n = 56):

This was given for the treatment of breast cancer. 112 patients also received palliative chemotherapy. 85 patients received hormonal therapy.

Symptomatic relief (n = 17) was given in the form of corticosteroids.

Outcomes:

Overall survival (OS) measured from the time of detection of brain metastases to death or to the end of the study.

Follow up:

Follow-up was closed 1 year after the end of the treatment period (i.e. December 2006).

All patients were followed until death or to the end of the study period. At this point 4/162 patients were alive. 114/162 patients had died as a result of brain metastases, 30/162 from systemic

metastases and 18/162 patients from non-breast cancer causes.

Results:

Median OS for all patients = 26 weeks (range: 1-520)

Median OS by method of treating brain metastases (BM):

Resection (n = 10): 82 weeks (range: 20-520)

RT overall (n = 145): 26 weeks (range: 1-508)

RT for 1 BM (n = 45): 44 weeks (range: 1-508)

RT for multiple BM (n = 100): 23 weeks (range: 1-444)

Chemotherapy (n = 112): 25 weeks (range: 1-520)

No chemotherapy (n = 50): 25 weeks (range: 1-508)

Symptomatic relief only (n = 17): 5 weeks (range: 1-144)

Median OS: premenopausal (n = 81) = 26 weeks

Median OS: postmenopausal (n = 81) = 25 weeks (nsd)

Median OS: < 40 years (n = 15) = 12 weeks

Median OS: > 40 years (n = 147) = 29 weeks (nsd)

Median OS: systemic metastases = 23 weeks (range: 1-508)

Median OS: no systemic metastases = 40 weeks (range: 1-520) (nsd)

Independent predictors for survival with univariate analysis:

Number of brain metastases (1 vs > 1) P < 0.025

Grading of breast cancer (I/II vs III/IV) P < 0.001

Radiation dose (< 30 Gy vs > 30 Gy) P < 0.001

KPS (< 60 vs > 60) P < 0.001

Predictors for survival with multivariate analysis:

Number of brain metastases (1 vs >1) P < 0.04

Size of primary breast tumour (I/II vs III/IV) P < 0.04

Radiation dose (< 30 Gy vs > 30 Gy) P < 0.001

KPS (< 60 vs > 60) P < 0.001

General comments:

This paper describes a moderate retrospective study of women with breast cancer and brain metastases treated at a single hospital between 1969 and December 1995.

Of 162 patients, 145 were treated with WBRT (10 of whom also received surgery) but 17 patients received symptomatic treatment only (corticosteroids).

49/162 patients had a single brain metastasis and 113/162 patients had multiple brain metastases. 27/162 patients had no other systemic metastases but the remainder had extracranial lesions.

Patients had brain metastases diagnosed by radionuclide scan (n = 26), CT scan or MRI.

Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups. Prognostic factors were tested by means of univariate and multivariate regression analysis.

Data are presented as point estimates with ranges. This is a very thorough analysis of data obtained retrospectively but the careful selection and low numbers in some sub-groups do render the results unreliable to some degree.

The authors point out that a patient with solitary metastases has a significantly better outcome, regardless of treatment protocol.

The best outcome was obtained by patients who, having good performance status and without systemic disease were treated with surgery. However, the patient number (n=10) was low and hence this result must be viewed with caution.

Levin *et al.* (2002)

Design: Retrospective case series (prognosis), evidence level: 3
Country: United States

Inclusion criteria:
None stated

Exclusion criteria:
None stated

Population:
Number of patients = 12, age range 30 to 58 years, median age = 48 years

Interventions:
Stereotactic radiosurgery. Median dose of 17 Gy (range: 15-18) was prescribed to 50% isodose.

Outcomes:
Survival.

Follow up:
Extent of disease was determined by T1 weighted MRI. Patients were evaluated clinically and with MRI every 2 -3 months for an unstated length of time.

At the close of the study (at the time of writing the report) there were 3/12 survivors and of the 9/12 patients had died 2 were from neurological causes, 6 with controlled brain disease and 1 of CNS and systemic disease progression.

Results:
Median KPS before treatment = 70 (range: 60-90)

Median OS = 11.5 months (range: 1-32)

5 patients exhibited no further signs of CNS disease and received no further treatment. 4 patients received further radiosurgery and 3 of these subsequently also received WBRT. 6 patients were given salvage therapy at a median duration of 8.5 months after SR. 1 patient developed a new symptomatic lesion and died 10 months after SR.

General comments:
This paper describes a retrospective review of case files of 12 breast cancer patients with brain metastases who had received gamma knife radiosurgery following treatment with high dose chemotherapy and autologous bone marrow transplant. Surgery had occurred between June 1996 and April 2002 at a single treatment centre.

The median number of lesions per patient = 4 (range 1-8)

Authors are of the opinion that giving SR is preferable to WBRT in patients who have previously received HD chemotherapy due to the reduced risk of additive neurotoxicity. Treatment with SR may at least allow a considerable delay before the necessity of giving WBRT.

This is a poor quality, low patient number study which offers little in the way of evidence. The

presence or absence of extracranial disease was not stated.

Liu *et al.* (2006)

Design: Retrospective case series (prognosis), evidence level: 3
Country: China (PRC)

Inclusion criteria:
 None stated

Exclusion criteria:
 None stated

Population:
 Number of patients = 48, age range 24 to 86 years, median age = 50 years

Interventions:
 WBRT (n = 48):
 Radiation was given with bilateral parallel opposed lateral fields. 10/48 patients received 30 Gy in 10 fractions, 10/48 patients received 37.5 Gy in 15 fractions and 11/48 patients received 40 Gy in 20 fractions.

Outcomes:
 Overall survival (OS) measured from the starting date of WBRT to death or last patient contact.

Follow up:
 Original extent of disease was identified by MRI or CT.

By the end of the study period, 42/48 patients had died.

Results:
 Median OS = 7.3 months
 Survival at 1 year = 37%
 Survival at 2 years = 20%

Median OS: KPS < 70 (n = 20) = 2.2 months
 Median OS: KPS 70-80 (n = 10) = 7.3 months
 Median OS: KPS 90-100 (n = 18) = 23.1 months P < 0.0001

Median OS: 1 brain metastasis (n = 21) = 14.5 months
 Median OS: >=2 brain metastases (n = 27) = 4.2 months P < 0.015

Median OS: RPA I (n = 11) = 23 months
 Median OS: RPA II (n = 17) = 10.2 months
 Median OS: RPA III (n = 20) = 2.3 months P < 0.0001

Median OS: ≤ 50 years (n = 24) = 10.2 months
 Median OS: > 50 years (n = 24) = 4.3 months P = 0.0452

Hence, univariate analysis showed that KPS, the number of brain lesions, RPA class and age were all significant prognostic factors for survival. In multivariate analysis KPS (P < 0.001 HR = 2.771 95%CI: 1.783-4.305) and number of brain metastases (P = 0.039 HR = 0.476 95%CI: 0.236-0.962) were the only statistically significant predictors of OS.

Symptoms were improved in 27 patients, remained stable in 15 patients but deteriorated in 6 patients.

Toxicities were noted in all patients but were mild: fatigue, nausea, scalp erythema and alopecia.

General comments:

This paper described a small retrospective study of patients treated for brain metastases from primary breast cancer at a single centre. WBRT was delivered to these patients between July 1988 and December 2004.

21/48 patients had a single metastasis, 27/48 had two or more lesions. 35/48 patients had extracranial metastases and 13/48 had solitary lesions.

Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups. Prognostic factors were tested by means of univariate and multivariate regression analysis. Data were presented in many cases as point estimates.

Mahmoud-Ahmed *et al.* (2002)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States

Inclusion criteria:

Treatment with WBRT only for brain metastases from BC

Exclusion criteria:

Incomplete medical records
 Patients undergoing surgical treatment
 Treatment with SR

Population:

Number of patients = 116, age range 33 to 99 years, median age = 50 years

Interventions:

112 patients received WBRT by the 'standard technique' but 3 patients received WBRT via a 'German helmet' and 1 by craniospinal route.

Most patients received a total dose of 3000 cGy in 10 fractions. The median total dose was 3000 cGy (range: 900 - 4500 cGy)

7 patients were given a boost with external beam RT with a median dose of 3900 cGy (range: 3600-4750 cGy)

6 patients discontinued treatment because of deterioration.

Outcomes:

Overall survival (OS) measured from the time of WBRT until time of death or last patient contact, Improvement in KPS as measured by withdrawal from steroid treatment (which was given to all patients prior to WBRT).

Follow up:

Brain metastases were confirmed by use of MRI or CT and these methods were used for follow-up after WBRT. No further details were given.

Only 60/116 patients had at least one follow-up MRI scan by which a treatment response could be assessed. One patient was lost to follow-up altogether.

Cause of death was only determined with certainty in 47 patients of which 10 died of intracranial metastases and 37 of other systemic metastases.

Results:

Median OS for all patients = 4.2 months

OS rate at 1 year = 17%
OS rate at 2 years = 2%

Median OS: KPS < 60 (n = 64) = 1.7 months
Median OS: KPS 70-80 (n = 26) = 4.8 months
Median OS: KPS 90-100 (n = 26) = 8.6 months P = 0.008

Median OS: RPA III (n = 27) = 1.7 months
Median OS: RPA II (n = 78) = 6.1 months
Median OS: RPA I (n = 11) = 8.1 months P = 0.015

Median OS: <3000 cGy (n = 18) = 0.4 months
Median OS: = 3000 cGy (n = 80) = 4.4 months
Median OS: > 3000 cGy (n = 18) = 7.7 months P=0.0001

Symptom relief:

78 patients were withdrawn from steroids after WBRT but re-initiated in 30 patients after the development of new symptoms.

Some patients experienced fatigue, headaches, alopecia, weakness, memory changes and, in one patient, necrosis. 71 patients experienced disease progression either from the primary cancer (n = 16) or systemically (n = 55).

Tumour response (n = 60):

30 patients had failure either locally or with new brain lesions. 5 of these patients received a second course of WBRT and had a median OS of 42 days (range: 0-143) thereafter. 7 patients were treated with intensity-modulated RT or SR and had a median OS of 146 days (range: 7-332) thereafter.

Age, control of primary tumour, control of systemic disease, presence of liver metastases, number of brain metastases, treatment era were not significant prognostic factors for OS. Multivariate analysis showed that KPS was the only significant factor

General comments:

This paper described a large retrospective study of women with breast cancer and brain metastases who received WBRT at a single treatment centre between 1984 and 2000.

79/116 patients had extracranial metastases. 20/162 patients had a single brain metastasis, 38/116 patients had 2-3 lesions, 50/116 had 4-9 lesions and 8/116 patients had more than 9 lesions.

Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups and the relative contributions to survival of potential prognostic factors.

Data are presented as point estimates and ranges which does not inform about the variance of that data or the statistical significance of conclusions made. The patient numbers are also too low in some sub-groups for comparisons to be statistically sound.

Authors admit to a confounding bias in one sub-group analysis: all the patients who received > 3000 cGy WBRT also had KPS >70, RPA II and controlled primary disease in 72%. This would have probably skewed the results in favour of a longer OS.

Muacevic *et al.* (2004)

<p>Design: Retrospective case series (prognosis), evidence level: 3 Country: Germany</p>
<p>Inclusion criteria: Breast cancer Histological evidence of brain metastases from breast cancer Maximum tumour dimensions of 3 cm Probable life expectancy of ≥ 3 months KPS ≥ 50 Stable primary tumour or in remission without systemic therapy</p>
<p>Exclusion criteria: Meningeal or ependymal tumour spread (seen by MRI or from CSF sample)</p>
<p>Population: Number of patients = 151, age range 35 to 78 years, median age = 60 years</p>
<p>Interventions: Stereotactic gamma knife radiosurgery (SR) performed by a single neurosurgeon on an outpatient basis.</p> <p>Mean minimum dose = 19 Gy \pm 4 Gy Mean maximum dose = 37 Gy \pm 4 Gy Mean no of isocentres = 4.8 \pm 3.1</p>
<p>Outcomes: Local tumour control: improved KPS, stable disease (SD), progressive disease (PD). Overall survival (OS).</p>
<p>Follow up: Baseline and follow-up MRI scans were made of all patients to determine disease extent and treatment effect.</p> <p>Follow-up examinations were made at 3 months and 6 months after SR and then every 6-9 months until death or to the end of the study. KPS was used to define patient improvement/deterioration. Tumour volume was calculated using a 'computerised planning system'.</p> <p>Patients who died with (1) stable extracerebral disease but progressive neurological dysfunction, (2) severe neurological disability and intercurrent illness or (3) progressive systemic and neurological disease were considered to have experienced neurological death.</p> <p>No patients were lost to follow-up. Median follow-up period was 8.3 months (range: 1 week to 55 months).</p> <p>110 patients had died at the time of last follow-up: 9 patients died of progressive CNS disease, 21 from neurological death, 8 from unknown causes and the remainder from progressive systemic disease.</p>
<p>Results: 117 patients had one SR session 28 patients had 2 SR sessions 5 patients had 3 SR sessions 1 patient had 4 SR sessions 1 patient had 5 SR sessions (NB patient total does not equal 151)</p> <p>Local brain tumour response rate = 94% Improved KPS after SR = 70%</p>

SD = 19%
PD = 11%

Median OS for all patients = 10 months
Median OS for patients with controlled systemic disease and no extracranial metastases = 34.9 months
Median OS for patients with RPA class I = 34.9 months (\pm 5.3)
Median OS for patients with RPA class II = 9.1 months (\pm 1.5)
Median OS for patients with RPA class III = 7.9 months (\pm 2.4)

Significant positive prognostic variables were KPS > 70 (P = 0.04) and RPA I classification (P < 0.0012) in multivariate analysis. Additionally, in univariate analysis, age > 65 years was a negative predictor of survival (P < 0.041). The presence of multiple metastases had no prognostic impact on treatment outcome.

11 patients experienced treatment related complications which were controlled with steroids. No patient died from treatment related cause or underwent surgery for a treatment related event.

General comments:

This paper describes a retrospective review of patients who had undergone stereotactic radiosurgery of metastatic brain tumours secondary to breast cancer between September 1994 and January 2003.

Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups and the association between survival and various prognostic factors.

63% of patients had multiple brain metastases and 37% single metastases. 133 patients (88%) had extracranial metastases. which had been surgically removed in 27 patients. The remaining 12% of patients may have had solitary lesions but this was not stated.

Patients had received surgery for tumours > 3cm (n = 30) or WBRT prior to (n = 37) or after (n = 9) SR. 113 patients had also received chemotherapy before SR.

Intermediate risk (RPA I) patients = 12%
High risk (RPA II) patients = 72%
Very high risk (RPA III) patients = 16%

Ogura *et al.* (2003)

Design: Retrospective case series (prognosis), evidence level: 3
Country: Japan

Inclusion criteria:
None stated

Exclusion criteria:
Patients with meningeal carcinomatosis
Patients who could not complete the entire treatment course
Patients who had received surgical resection before RT

Population:
Number of patients = 36, age range 29 to 78 years, median age = 52 years

Interventions:
For patients with life expectancy > 6 months WBRT was given at 50 Gy in 25 fractions (long

course). Other patients received WBRT at 30 Gy in 10 fractions (short course).

10 patients received boost RT, of which 8 had conventional external beam therapy at 10-22 Gy and 2 patients received SR using a linear accelerator.

Median total tumour dose overall = 34 Gy (range: 20-62 Gy).

Outcomes:

Overall survival (OS), Tumour response: complete response (CR), partial response (PR), progressive disease (PD).

Follow up:

Patients were followed from initial diagnosis to death or close of study, at the end of which 5/36 patients were alive.

Initial diagnosis of brain metastases was made by CT or MRI but no histology was available.

2 patients developed neurocognitive disorder after treatment: 1 developed leukoencephalopathy after 2 years and the other showed diffuse brain atrophy after 1 year.

Results:

Median OS (n = 36) = 7.9 months

Survival at 1 year = 40%

Median OS: Age < 53 years (n = 19) = 13 months

Median OS: Age ≥ 53 years = 6.7 months P = 0.048

Median OS: Bone (or no) other metastases (n = 14) = 13 months

Median OS: Extracranial metastases (n = 22) = 5 months P = 0.0013

Only age and the presence of uncontrolled extracranial metastases, other than in bone, were significant factors in predicting OS. Performance status was not significantly different but this factor was only categorised as patients whose WHO PS = 0 or patients whose PS ≥ 1.

Tumour control measured 1 month after WBRT (n=32):

CR = 5 (15%)

PR = 21 (66%)

No change = 6 (19%)

PD = 0

15 patients showed intracranial failure: 9 patients had tumour recurrence at the original site, 4 patients developed CNS tumours elsewhere and 3 patients had tumour spread to the meninges.

Mean duration of response = 5 months.

General comments:

This paper describes a small retrospective study of women with breast cancer and brain metastases who were given WBRT at a single centre between June 1993 and April 2001.

4/36 patients had a single metastasis and 32/36 had multiple lesions. Extracranial metastases were present in 26/36 patients.

Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups. The influence of various prognostic factors on survival was reported but the methodology was not given (assumed to be univariate and/or multivariate analysis). Data were given as point estimates.

The 1 year survival rate may be better than would have been achieved in practice since those patients with meningeal spread were excluded from this study.

Authors found no significant difference in local control or survival between patients receiving different treatment courses.

Pieper *et al.* (1997)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States

Inclusion criteria:

None stated

Exclusion criteria:

Patients who had brain metastases resected due to recurrence or progression after non-surgical intervention

Population:

Number of patients = 63, age range 30 to 71 years, median age = 50 years

Interventions:

Gross total resection confirmed by negative margins at the time of surgery or immediate post-operative neuroimaging (n = 54)

Subtotal resection for patients presenting with multiple metastases (n = 9)

Outcomes:

Improvement in performance status (KPS). Overall survival (OS)

Follow up:

Initial evaluation was performed by neuroradiologists and took the form of CT and/or MRI scans.

Follow-up after surgery was by means of clinical examination or by correspondence with patients and their physicians. No patients were lost to follow-up.

55/63 patients died during the follow-up period. 48 patients died of disease progression, either neurological (n = 20), systemic (n = 24) or both (n = 4). Cause of death for the remaining 7 patients is not reported.

Results:

Improvement in performance status (KPS):

Before surgery:

45/63: KPS ≥ 90

11/63: KPS = 80

5/63: KPS = 70

2/63: KPS = 60

After surgery:

11/63 patients had improved KPS

4/63 patients had worsened KPS

48/63 patients had no change in KPS

Following surgery, 62/63 patients received adjuvant therapy: 54 received WBRT (33 with chemotherapy) and 8 patients received chemotherapy only. 21 patients received chemotherapy both pre- and post-operatively.

10 patients developed distal metastases and 11 patients had local recurrence. 7 patients

developed leptomeningeal disease.

Median OS = 16 months (95%CI: 11-22)
Survival at 3 years = 22% (95%CI: 14-35)
Survival at 5 years = 17% (95%CI: 9-29)

Median OS: Active systemic disease = 8 months
Median OS: Controlled systemic disease = 15 months
Median OS: No evidence of systemic disease = 26 months P = 0.0003

Median time to recurrence = 15 months (95%CI: 12-24)

Prognostic factors for survival:

10-year increase in age: RR = 1.34 (95% CI: 1.03-1.73) P = 0.028 (univariate) or RR = 1.97 (95% CI: 1.16-3.34) P = 0.012 (multivariate)

No active disease vs active disease: RR = 0.28 (95%CI: 0.14-0.53) P = 0.0001 (univariate) or RR = 0.14 (95%CI: 0.06-0.35) P < 0.0001 (multivariate)

Controlled disease vs active disease: RR = 0.14 (95%CI: 0.11-0.67) P = 0.0052 (multivariate)

2-year increase of interval to development of brain metastasis: RR = 1.16 (95%CI: 1.02-1.32) P = 0.026 (univariate).

General comments:

This paper describes a retrospective review of data from breast cancer patients who had undergone resection of brain metastases as primary therapy between April 1983 and May 1992. 97% of these patients had received surgery within 2 weeks of diagnosis.

Survival analysis was by the method of Kaplan-Meier and comparison between curves was by the log rank test. Potential prognostic factors were tested by univariate and multivariate (Cox's proportional hazards model) analyses.

18/63 patients had solitary metastases. 55/63 patients had single metastases and 8 patients had multiple brain lesions. The total number of metastases treated was 75.

18/63 patients had active systemic disease at the time of surgery, 17/63 patients had stable systemic disease and 28 patients had no evidence of systemic disease.

Authors maintain that analysis of the data shows that the patterns of death over time differ in patients that have systemic disease progression (Group A) compared with patients who have neurological disease progression (Group B). The rate of increase and magnitude is significantly greater in the period 0-6 months after surgery for Group A, but then declines rapidly. The peak of mortality for group b is at the end of the second year whereas survival is high in the early post-operative months.

Multivariate analysis also showed a 60% lower risk for patients that received WBRT after surgery compared with patients who did not. Chemotherapy made no significant difference in this respect.

Authors conclude that surgery is beneficial as part of a combined treatment early in the treatment pathway particularly for patients with a good performance status and controlled or absent systemic disease.

Rivera *et al.* (2006)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States

<p>Inclusion criteria: Bidimensionally measurable brain metastasis from breast cancer Newly diagnosed Refused RT or were neurologically stable or had tumour progression or recurrence after WBRT or SR Life expectancy of > 8 weeks Zubrod performance status ≤ 2 Adequate renal, liver and bone marrow function (definitions given).</p>
<p>Exclusion criteria: Prior treatment with temozolomide or capecitabine Rapidly progressing visceral disease Serious medical condition (not defined).</p>
<p>Population: Number of patients = 24, age range 32 to 77 years, median age = 50 years</p>
<p>Interventions: Capecitabine (C) given orally in 2 divided doses and Temozolomide (T) given orally once daily. Concomitant daily doses were given on days 1-5 and 8-12 with cycles repeated every 21 days. Patients were divided into treatment groups based on dosage:</p> <p>Dose level 0 (n = 6): C at 1800 mg per m² + T at 75 mg per m² Dose level 1 (n = 6): C at 1800 mg per m² + T at 100 mg per m² Dose level 2 (n = 8): C at 2000 mg per m² + T at 100 mg per m² Dose level 3 (n = 4): C at 2000 mg per m² + T at 150 mg per m²</p> <p>Patients were treated until disease progression or unacceptable toxicity. Treatment was withheld for dose-limiting toxicities (defined) and was then resumed at the same or a lower dose level when the toxicity was resolved.</p>
<p>Outcomes: Primary: to determine the maximum tolerated dose of temozolomide and capecitabine</p> <p>Secondary: response rates, response duration (RD), tumour response: Complete response (CR), Partial response (PR), Minor response or stable disease (SD), Progressive disease (PD), Not evaluable (NE).</p>
<p>Follow up: Before treatment patients were given a full clinical examination, assessment of performance status, radiological studies, MRI, complete blood count, urinalysis, blood chemistry, and pregnancy test.</p> <p>Complete blood cell and differential counts were tested every week during the study and toxicity was assessed on day 1 of every three week cycle. Imaging (MRI) was repeated every 6 weeks. Neurocognitive functioning was tested by a trained psychometrician one month after treatment had begun and for some patients (n = 7) at the end of the study. Symptoms and quality of life were assessed during follow-up and at the end of the study.</p> <p>17/24 patients were taken off study with disease progression in the brain and 5/24 for disease progression elsewhere. None were taken off for toxicity.</p>
<p>Results: Median number of treatment cycles per patient = 4 (range: 1-16 cycles)</p> <p>Tumour response: Dose level 0 (n = 6): CR (n = 1) PR (n = 1) SD (n = 2) PD (n = 2) NE (n = 0) Dose level 1 (n = 6): CR (n = 0) PR (n = 1) SD (n = 3) PD (n = 1) NE (n = 1)</p>

Dose level 2 (n = 8): CR (n = 0) PR (n = 1) SD (n = 5) PD (n = 1) NE (n = 1)
 Dose level 3 (n = 4): CR (n = 0) PR (n = 0) SD (n = 1) PD (n = 3) NE (n = 0)
 Total CR = 1 (this patients had not received prior WBRT and was on dose level 0)
 Total PR = 3 (1 of these patients had not received prior WBRT, 2 patients had received prior WBRT)
 Total SD = 11
 Total PD = 7
 Total NE = 2

Grade 3/4 adverse events:

Dose level 0 (n=6): neutropenia (n=3), headache (n=1) constipation (n=1)
 Dose level 1 (n = 6): fatigue (n = 1), vomiting (n = 1), headache (n = 1), constipation (n = 1)
 Dose level 2 (n = 8): fatigue (n = 2), neutropenia (n = 2), thrombocytopenia (n = 2)
 Dose level 3 (n = 4): fatigue (n = 2), vomiting (n = 2), neutropenia (n = 2), thrombocytopenia (n = 1)

Median RD = 8 weeks (range: 6-64)
 Median TTP in brain = 12 weeks (range: 3-70)

Neurocognitive function:

Improvements were noted in attention span (P = 0.047) and emotional function (P = 0.016) but there were no significant differences between baseline and end-of-study assessments.

General comments:

This paper was primarily a prospective, phase I dose finding study but which included details of tumour response and adverse events. Patients were treated with chemotherapy at a single institution.

14/24 patients were newly diagnosed with brain metastases, all of whom had declined WBRT. 10/24 patients had recurrent metastases, 8 of whom had received prior WBRT. All patients had multiple metastases which were inoperable and not amenable to SR.

Although relatively small and not designed for the purpose, nevertheless this phase I study produced useful data regarding tumour response and adverse events. There were no statistical analyses and data were presented straightforwardly as point estimates with ranges. Unfortunately only a small sub-set of patients were examined at the end of the study period and there was no long term follow-up.

Authors conclude that this treatment regime may provide an active and well tolerated alternative to WBRT in the treatment of patients with multiple brain metastases.

Rosner *et al.* (1986)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States

Inclusion criteria:

None stated

Exclusion criteria:

14 patients were excluded for the following reasons:
 Meningeal carcinomatosis
 Orbital metastases
 Primary glioblastoma
 CNS bleeding
 Multiple primaries

<p>Population: Number of patients = 100, age range 32 to 82 years, median age = 52 years</p>
<p>Interventions: CFP (n = 52) Cyclophosphamide at 150 mg per m² + 5'-fluorouracil at 300 mg per m² i.v. daily for 5 days given every 5 weeks + prednisone tapered from 40 mg to 10 mg maintenance.</p> <p>CFPMV (n = 35): 5'-fluorouracil at 500 mg per m² + methotrexate at 25 mg + vincristine at 1 mg i.v. once a week + prednisone and cyclophosphamide orally daily</p> <p>MVP (n = 7): Methotrexate at 25 mg + vincristine at 1 mg i.v. once a week + prednisone</p> <p>CAP (n = 6) Cyclophosphamide at 400 mg per m² + doxorubicin at 40 mg per m² i.v. on day 1 every 4 weeks + prednisone.</p> <p>Chemotherapy was administered until disease progression. Some patients were given second or third line chemotherapies after progression or relapse and others received WBRT.</p>
<p>Outcomes: Tumour response: complete response (CR), Partial response (PR), Stable disease (SD), No response (NR). Overall survival (OS) measured from time of therapy initiation. Response duration (RD).</p>
<p>Follow up: Original diagnosis of brain metastases was from objective clinical findings and/or technetium 99 scans (1970-1976) and/or CT (post-1977). Baseline tests also included neurological functional status assessment.</p> <p>Evaluation of patients for CNS and extracranial disease was performed every 8-10 weeks during therapy.</p> <p>At September 1985 89/100 patients had died, 5 patients were still receiving chemotherapy and 6 patients were lost to follow-up.</p>
<p>Results: Tumour response: CR = 10 PR = 40 ORR (CR + PR) = 50 SD = 9 NR = 41</p> <p>Sub-group analysis by diagnostic method: ORR for patients diagnosed by radionuclide scan (n = 49) = 25 ORR for patients diagnosed by CT (n = 51) = 25 nsd</p> <p>Sub-group analysis by chemotherapy regime (n/%): ORR for CFP (n = 52) = 27 (52%) ORR for CFPMV (n = 35) = 19 (54%) ORR for MVP (n = 7) = 3 (43%) ORR for CAP (n = 6) = 1 (17%) There was no significant difference between CFP and CFPMV. Other comparisons were made but the sub-group size is too small to draw such conclusions.</p>

Positive response were obtained from:
 13/21 patients previously treated with endocrine therapy
 7/14 patients previously treated with chemotherapy
 9/28 treated with endocrine and chemotherapy sequentially.

All 50 patients that responded to therapy presented clinical improvement of CNS symptoms and neurological functional status. 20 patients became asymptomatic during remission.

Median RD for responders (n = 50) = 7 months (range: 2-72)

Median OS: all patients (n = 100) = 5.5 months
 Median OS: with CR (n = 10) = 39.5 months (range: 6-62)
 Median OS: with PR (n = 40) = 10.5 months (range: 3-78)
 Median OS: with SD (n = 9) = 6.5 months (range: 3-18)
 Median OS: non-responders (n = 41) = 1.5 months (range: 1-5) P < 0.001 cf responders

Survival at 1 year+ = 31%

14/17 patients who received WBRT after failure of chemotherapy failed to respond to this treatment.

General comments:

This paper describes a retrospective review of 100 patients treated by chemotherapy (4 regimes) from 1970 to June 1985 at a single US centre. All patients had brain metastases from primary breast cancer.

19 patients had extracranial metastases diagnosed at study entry whereas 2 had CNS lesions only. The remaining 79 patients had one or more established extracranial metastatic sites.

This is a very thoroughly reported study but which has the usual limitations of being retrospective. Data are presented as point estimates with ranges.

The authors conclude that brain lesions, possibly due to the formation of new accessible vasculature, may be sensitive to water-soluble chemotherapeutic drugs unlike areas of the brain protected by the BBB.

Wroski *et al.* (1997)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States

Country: United States

Inclusion criteria:

None stated

Exclusion criteria:

None stated

Population:

Number of patients = 70, age range 27 to 79 years, median age = 50 years

Interventions:

En bloc resection of tumour (n = 33)

Piecemeal resection of tumour or removal with a surgical aspirator (n = 37)

Dexamethasone was given to all patients after diagnosis and for a minimum of 3-4 days before surgery.

15 patients received whole brain radiotherapy (WBRT) before craniotomy (n = 15) and 47 patients received WBRT after craniotomy. There are no details of dosage or administration.

Outcomes:

Overall survival (OS) calculated as the period of time since the first craniotomy.

Follow up:

Records were available for all patients as far as December 30th 1995 giving a minimum follow-up of 2 years.

By the end of the study, 5 patients were alive.

51% patients died of neurological causes and 30% died from systemic disease. Cause of death was unknown for 8 patients.

Results:

68/70 patients had metachronous (median interval of 28 months range: 2-182) diagnoses of breast cancer and brain metastasis. 2/70 patients had synchronous diagnoses.

2/70 patients were found to have brain metastases from malignant breast lesions other than ductal or lobular carcinoma.

4/70 patients had other distant metastases at the time of primary diagnosis and 2/70 women were inoperable.

54/70 patients had a single brain metastasis and 16/70 patients had multiple brain metastases. The actuarial survival was not significantly different between these sub-groups.

16/70 patients had meningeal carcinomatosis. The actuarial survival for this group was significantly lower than for other patients: median OS = 5.6 months (95% CI: 3.1-15.8) P < 0.0016

Method of tumour removal (i.e. en bloc vs piecemeal) did not impact on median OS.

Patients receiving WBRT after craniotomy (n = 47) had a longer median OS than patients receiving WBRT before craniotomy (n = 15): 15.8 months vs 6.3 months (P < 0.03). However, when median OS was calculated from the time of diagnosis of brain metastasis the groups did not differ significantly

Patients with positive hormonal status (n = 22) had a longer median OS than patients with negative hormonal status (n = 20): 25 months (95%CI: 9.6-32) vs 12.5 months (95%CI: 4.6-19.8) P = 0.04

Median OS for all patients = 13.9 months (95%CI: 10.3-18.8). 4 patients died within 30 days of surgery.

Survival rate at 1 year = 55.3%
Survival rate at 2 years = 25.7%
Survival rate at 3 years = 18.6%
Survival rate at 5 years = 7%

In multivariate analysis of all possible prognostic factors (including tumour size), only two variables were found to be of favourable significance with respect to survival: adjuvant WBRT after craniotomy (P = 0.0003) and the absence of meningeal carcinomatosis (P = 0.0007).

General comments:

This paper describes a retrospective review of patients who had undergone surgical resection of metastatic brain tumours secondary to breast cancer between January 1974 and December 1993.

The patient group includes those with solitary metastases and those with single or multiple lesions as part of widespread metastatic disease. In addition, 27/70 patients had recurrent brain metastases.

Survival analyses were by the method of Kaplan-Meier. Appropriate statistical methodology was used to analyse the comparisons of survival between sub-groups and the association between survival and various prognostic factors.

This paper provides a reasonable analysis of data from a small group of patients but is retrospective and hence limited in its evidential value.

In the analysis of survival four patients who had died within 30 days of surgery were excluded. It is not possible to say whether their exclusion may have impacted on statistical findings. For example, would large tumour size have had an impact on survival (all four patients had tumours of 5cm)?

Oberhoff *et al.* (2001)

Design: Phase II study (prognosis), evidence level: 3

Country: Germany

Inclusion criteria:

Age ≥ 18 years

Histologically or cytologically confirmed diagnosis of breast cancer

At least one Bidimensionally measurable brain metastasis

Prior adjuvant and/or palliative endocrine or cytotoxic therapies allowed

Sufficient liver, kidney and bone marrow function

WHO performance status 0-2

Life expectancy > 3 months

Written informed consent.

Exclusion criteria:

Concomitant endocrine treatment or chemotherapy

Simultaneous RT (except for bone metastases)

Prior WBRT.

Population:

Number of patients = 24, age range 36 to 74 years, mean age = 58 years

Interventions:

Topotecan was given at 1.5 mg per m² per day as a 30 minute infusion for 5 days every 21 days. 10/24 patients also received corticosteroids.

Treatment was continued until disease progression at which point RT was administered as second line.

Outcomes:

Tumour response: Complete response (CR), Partial response (PR), Stable disease (SD), Disease progression (PD), Not evaluable (NE). Adverse events. Duration of response (RD). Overall survival (OS).

Follow up:

Response evaluation was performed prior to treatment initiation and then prior to every third cycle using a CT or MRI scan.

Adverse events were assessed before each treatment cycle using routine clinical and laboratory tests.

3/24 patients were excluded from the study for personal reasons (n = 2) and glioblastoma (n = 1). 5 patients who had completed only one cycle of treatment were excluded from the response evaluation. The reasons for non-completion were because of side effects (n = 1) or rapid tumour progression (n = 4).

Results:

Median number of treatment cycles per patient = 3 (range: 1-11)

Median time to best response = 76 days (range: 35-161)

Tumour response (n = 16):

CR = 1

PR = 5

SD = 5

PD = 5

NE = 0

Median RD = 124 days (range: 35-151 days)

Median duration of SD = 45 days (range: 41-161 days)

Median OS = 6.25 months (95% CI: 4.7-9.6 months, range: 1.25-13.2 months)

Grade 3/4 adverse events (for 93 treatment cycles):

Haemoglobin = 11/2

White blood cells = 35/17

Neutrophils = 11/12

Platelets = 26/10

Stomatitis = 3/0

Constipation = 7/1

Sensorium = 1/0

Pain = 2/1

Fever = 2/0

Infection = 5/0.

General comments:

This paper describes a prospective phase II study of 24 patients treated with topotecan chemotherapy for brain metastases from breast cancer at a single institute between June 1998 and October 1999.

Survival analyses were by the method of Kaplan-Meier.

18/24 patients had extracranial metastases and in 10 of these patients disease was present in more than one other organ.

This is a well reported but rather small and statistically underpowered pilot study.

Updated evidence 6.5

Summary

Six papers were identified to update the evidence on the management of brain metastases. None of these studies were of high quality being mostly low patient number, retrospective and non-comparative. The number of patients across all studies totalled 1,469.

Two papers on whole brain radiotherapy (WBRT) presented the results from recursive partition analyses undertaken predominantly to determine prognostic factors for survival. Viani *et al.* (2007) identified prior surgical resection ($P < 0.0001$) absence of extracranial metastases ($P < 0.0001$) and RPA class I ($P < 0.0001$) whilst Johansen *et al.* (2008) found only having single vs multiple brain metastases ($P < 0.01$) to be of significance. Viani *et al.* concluded that patients with the best survival prognosis were those who were RPA class I, treated with local resection followed by WBRT, with a single brain metastasis, higher performance status and controlled extracranial disease.

According to one retrospective study (Akyurek *et al.*, 2007) stereotactic radiosurgery (SRS) can be given as first line treatment of cerebral metastases and, in terms of overall survival or tumour response, is comparable with SRS as salvage therapy following disease progression with WBRT.

Lassman (2006) presented very limited evidence suggesting that high dose intravenous methotrexate addressed both parenchymal and leptomeningeal disease with acceptable toxicity whilst a small phase II study (Trudeau, 2006) found that stable disease in 3/19 patients was the best achievable response to treatment of cerebral metastases with oral temozolomide.

One retrospective case series (Rudnicka *et al.*, 2007) addressed the treatment of leptomeningeal metastases (LM) secondary to breast cancer and found that chemotherapy appeared to be crucial in the multimodal treatment of LM and that both intrathecal and intravenous chemotherapy improved patient survival. WBRT may have been shown in other studies to have improved quality of life but had a questionable effect on survival for these patients.

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Viani GA., Castilho MS., Salvajoli JV., Pellizzon AC., Novaes PE., Guimarães FS., Conte MA and Fogaroli RC (2007) Whole brain radiotherapy for brain metastases from breast cancer: estimation of survival using two stratification systems. *BMC cancer* **7**: 53-

Johansen R., Westin AA., Bofin AM and Lundgren S (2008) Outcome of whole-brain irradiation for breast cancer patients. *Acta Oncol* **47**: 261-266

Evidence tables

Question: Patients with solitary, single or multiple brain or leptomeningeal metastases
Created by: Karen Francis on 29/07/08

Trudeau <i>et al.</i> (2006)
<p>Design: Phase II study (therapy). Evidence level: 3 Country: Canada (federal state, Commonwealth Realm)</p>
<p>Inclusion criteria: Locally advanced or metastatic breast cancer At least one bidimensionally measurable lesion ECOG status ≤ 2 Aged ≥ 16 years Prior adjuvant chemotherapy and up to 2 regimes for advanced disease permitted Documented brain metastases either newly diagnosed or previously treated > 4 weeks previously Ability to take oral drugs Informed consent</p>
<p>Exclusion criteria: Pregnant or lactating Women unwilling to take effective contraception if of child-bearing age Previous or concurrent malignancies (except CIS cervix or bladder, or non-melanoma skin) unless > 5 years ago and believed to be cured No concurrent experimental drugs or anti-cancer therapy</p>
<p>Population: Number of patients = 19. Age range 43 to 75 years. Median age = 54 years</p>
<p>Interventions: Oral temozolomide (TEM) at 150 mg per m^2 on days 1-7 and 15-21 every 28-day cycle.</p> <p>Treatment was discontinued in the case of disease progression, serious toxicity or at the patient's request. The duration of therapy depended on the best response: complete response (2 cycles), partial response (4 cycles after establishment of stable disease or until disease progression), stable disease (maximum of 6 cycles). Treatment delays dosage reductions were applied for therapy-related toxicities (described).</p>
<p>Outcomes: Overall tumour response (ORR = CR + PR) complete response (CR) partial response (PR) response duration (RD) time to progression (TTP) and adverse events</p>
<p>Follow up: Baseline investigations included medical history, physical examination, toxicity screening from previous therapy, haematology, biochemistry, chest X-ray, abdominal CT scan, bone scan.</p> <p>During treatment, follow-up included biochemistry and physical examination on day 1 of each cycle, weekly blood counts for the first two cycles and then days 1 and 15 thereafter. Tumour response was assessed at the end of alternate cycles and toxicity was evaluated after each cycle.</p> <p>Two patients discontinued treatment due to toxicity (grade 4 lethargy, grade 2 anorexia and nausea in one patient and grade 2 anaemia, thrombocytopenia and leukopenia in the other). 15 patients discontinued due to disease progression and one patient died on study due to disease progression whilst another was withdrawn by the investigator.</p>
<p>Results: Efficacy (n=18): CR = 0 PR = 0 SD = 3 Range of RD in patients with SD = 2.7 to 5.6 months</p>

In those patients with brain lesions no tumour response was seen

Median TTP = 1.8 months

General comments:

This paper describes a small phase II study of patients with breast cancer and who may have had brain metastases. Patients were given temozolomide, a drug which crosses the blood-brain barrier and has been used in the treatment of brain tumours. In the event, 5/17 women had brain metastases. 12/17 women had three or more sites of metastatic disease and the majority also had bone, lung or nodal disease.

Accrual was terminated prematurely due to the lack of treatment response in this group and the authors concluded that they could not recommend temozolomide for heavily pre-treated breast cancer patients, specifically for treatment of brain metastases.

Lassman *et al.* (2006)

Design: Retrospective case series (therapy) Evidence level: 3

Country: United States of America

Inclusion criteria:

Patients who were treated with at least one cycle of rapid infusion high dose i.v. methotrexate (MTX) for CNS metastases

Exclusion criteria:

None stated

Population:

Number of patients = 32 (including 1 male). Age range: 33 to 76 years. Median age =52 years

Interventions:

MTX at 3.5 g per m² (n=30) at 4 g per m² (n=1) or at 2.5 g per m² (n=1) as a 3-4 hour infusion. In addition, leucovorin rescue, hydration and urine alkalinisation accompanied treatment
Treatment was given every other week until disease progression.

Subsequent doses for those having received 3.5 g per m² were reduced in response to toxicity or concurrent medical disease. The patient on 4 g per m² received only one dose and the patient on 2.5 g per m² remained on this dose for 13 cycles.

Outcomes:

Objective response rate (ORR = CR + PR) complete response (CR) partial response (PR) stable disease (SD) disease progression (PD) overall survival (OS)

Follow up:

Tumour response was assessed was by contrast enhanced CT scans (if in CNS parenchyma) and/or cytological examination of CSF or serial contrast MRI (if in leptomeninges). Two patients withdrew due to unacceptable, though reversible, toxicity.

Results:

9 patients had leptomeningeal disease, 14 had parenchymal disease and 9 had both. Total number of cycles = 141 (mean of 4.4 with range: 1-13).

Efficacy (n=32):

CR = 0

PR = 9 (3 patients with parenchymal disease, 5 with leptomeningeal disease, 1 with both)

ORR = 28%

SD = 9 (5 with parenchymal disease, 2 with leptomeningeal disease, 2 with both)

<p>PD = 14 (1 with parenchymal disease, 7 with leptomeningeal disease, 6 with both)</p> <p>Prior treatment with low dose MTX did not correlate with response.</p> <p>Median OS after 1 cycle (n=32) = 19.9 weeks (range: 2.9-135.4+)</p> <p>Median OS for patients with leptomeningeal disease = 12.6 weeks (range: 2.9-135.4+)</p> <p>Median OS for patients with parenchymal disease = 25.4 weeks (range: 11-58)</p> <p>Median OS for all patients from diagnosis = 53.7 weeks (range: 6.6-265.6)</p> <p>Median OS for patients receiving MTX only (n=23) = 20.1 weeks (range: 2.9-135.4)</p> <p>Grade 3/4 adverse events:</p> <p>Anaemia = 13</p> <p>Leukopenia = 8</p> <p>Thrombocytopenia = 8</p> <p>Raised transaminase = 12</p> <p>Hyponatraemia = 4</p> <p>Raised creatinine = 1</p> <p>Confusion = 7</p> <p>Seizure = 5</p> <p>Hypoxia = 2</p> <p>TIA = 1</p> <p>Small bowel obstruction = 1</p>
<p>General comments:</p> <p>This paper describes a retrospective review of case files of 32 patients who were treated with at least one cycle of rapid infusion high dose i.v. methotrexate for CNS metastases between September 1999 and April 2003. 29/32 patients had breast cancer.</p> <p>This retrospective review provides very little strong evidence since, other than being a non-comparative study, 9/32 patients were also receiving concurrent treatment directed towards the CNS disease including RT, intrathecal chemotherapy or CNS penetrating chemotherapy (i.e. capecitabine). This makes it impossible to assess the response to the intervention in question. If these patients were excluded from the efficacy analysis a partial response was seen in 5/23 (22%) of the remainder of the study population.</p> <p>The authors concluded that high dose i.v. MTX addressed both parenchymal and leptomeningeal disease with acceptable toxicity for patients with metastatic breast cancer.</p>

Akyurek <i>et al.</i> (2007)
Design: Retrospective case series (therapy). Evidence level: 3 Country: United States of America
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 49. Age range: 34 to 80 years. Median ages: 50-55 years (SRS-salvage)
Interventions: [1] Primary stereotactic radiosurgery (SRS) (n=34) [2] Salvage SRS (n=15)

SRS was delivered with a median dose of 18 Gy (range: 14-20) in a single session. Median isocentre dose was 21.1 Gy (range: 16.4-25).

Outcomes:

Tumour response, overall survival (OS), distant brain metastases-free survival (DBMFS) prognostic factors.

Follow up:

Baseline investigations included complete blood counts, serum chemistries, CT of chest abdomen and pelvis and bone scan. Serial MRI was used for follow-up assessment of tumour response which was undertaken every 1-3 months.

Results:

Survival (n=49):

Median OS with a median of 12 months (range: 5-50) follow-up = 19 months

1 year survival rate = 59%

2 year survival rate = 46%

Median OS for primary SRS (n=34) = 25 months

Median OS for salvage SRS (n=15) = 14 months

1 year survival rate for primary SRS = 60%

2 year survival rate for primary SRS = 55%

1 year survival rate for salvage SRS = 56%

2 year survival rate for salvage SRS = 23% (NSD between groups)

Prognostic factors for survival:

KPS \geq 90 vs $<$ 90 (P = 0.02)

Score index for radiosurgery \geq 60 vs $<$ 60 (P = 0.001)

Pre-menopausal vs post-menopausal (P = 0.003)

Estrogen receptor +ve vs -ve (P = 0.04)

Efficacy:

1 year local control rate for brain tumour for primary SRS = 79%

2 year local control rate for brain tumour for primary SRS = 49%

1 year local control rate for brain tumour for salvage SRS = 77%

2 year local control rate for brain tumour for salvage SRS = 46% (NSD between groups)

Prognostic factors for local tumour control:

None of the prognostic factors tested (number of metastases, tumour volume, SRS dose or cone diameter) were significant.

DBMFS:

1 year DBMFS for all patients = 69%

1 year DBMFS for primary SRS = 64%

1 year DBMFS for salvage SRS = 57% (NSD between groups)

Prognostic factors for DBMFS:

Primary controlled disease (P = 0.03)

Age \geq 50 years vs $<$ 50 years (P = 0.02)

Estrogen receptor +ve vs -ve (P = 0.05)

1 year freedom from the requirement for WBRT = 62%.

General comments:

This paper presents the findings from a retrospective review of case files of patients treated with

Linac stereotactic radiosurgery for brain metastases secondary to breast cancer. Patients were treated between July 2000 and September 2005 at a single centre. Some patients were being treated for the first time whilst others were receiving salvage therapy after experiencing disease progression after whole brain radiotherapy.

According to recursive partitioning analysis, 4 patients were RPA class I, 44 were class II and 1 was class I at baseline. 23 patients had a single metastasis (17 in the SRS group), 19 had 2 or 3 metastases (16 in the SRS group) and 7 had 4 or more metastases (1 in the SRS group). The majority of patients (90%) had extracranial disease.

This was a comparative study but not randomised. There was strong selection bias since the patients receiving salvage therapy may have had a worse prognosis and therefore this is not a fair comparison. Since WBRT may be associated with severe adverse events, often apparent some considerable time after treatment, the authors concluded that SRS was a good primary treatment but could be also offered as salvage therapy.

Johansen <i>et al.</i> (2008)
Design: Retrospective case series (therapy). Evidence level: 3 Country: Norway
Inclusion criteria: Patients with primary breast cancer and brain metastases
Exclusion criteria: Patients with cranial metastases, meningioma or glioblastoma Patients with primary lung cancer or cervical cancer
Population: Number of patients = 99. Age range: 30 to 80 years (start of WBRT). Median age = 57 years
Interventions: All patients received whole brain radiotherapy (WBRT) using 6 MV photons from a linear accelerator where 30 Gy in 10 fractions or 20 Gy in 5 fractions were given.
Outcomes: Survival, prognostic factors.
Follow up: -
Results: Survival (n=99): Median survival for all patients = 5.3 months (95%CI: 0.3-157) Median OS for patients with endocrine receptor +ve tumour = 5.2 months (95%CI: 1.8-7.6) Median OS for patients with endocrine receptor -ve tumour = 4.8 months (95%CI: 1.9-7.6) (NSD between groups) 1 year survival rate = 29% 2 year survival rate = 11% Prognostic factor for survival by univariate analysis: Disease-free interval (from primary tumour to first metastasis) (P = 0.02) Brain metastases-free interval (0-22 months vs > 22months) (P = 0.03) WBRT dosage (\leq 20 GY vs \geq 30 Gy) (P < 0.01)

<p>Prognostic factor for survival by multivariate analysis: Single vs multiple metastases (P < 0.01)</p> <p>Median OS for patients with single brain metastasis = 13.3 months (95%CI: 0.0-28.3) Median OS for patients with multiple brain metastases = 4.5 months (95%CI: 2.8-6.2)</p> <p>Median OS for RPA class I = 8 months (95%CI: 1-157) Median OS for RPA class 2 = 6.5 months (95%CI: 1.3-92) Median OS for RPA class 3 = 3.5 months (95%CI: 0.3-92) (NSD between groups)</p>
<p>General comments: This paper presents the findings from a retrospective review of case files of patients treated with WBRT at a single centre between January 1988 and September 2004. 21 of these patients had undergone surgery and 2 gamma knife RS. According to recursive partitioning analysis, 17 patients were RPA class 1, 19 patients were RPA class 2 and 63 patients were RPA class 3. 18 patients had a single brain metastasis and 81 patients had multiple brain metastases. 68% of patients had extra-cranial metastases.</p> <p>The authors concluded that prior knowledge of the prognostic factors that influenced survival may be important. Patients with multiple metastases had a significantly worse survival with treatment. This paper offers only limited evidence as a non-comparative, retrospective study.</p>

Viani <i>et al.</i> (2007)
Design: Retrospective case series (therapy). Evidence level: 3 Country: Brazil
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 174
Interventions: Whole brain radiotherapy (WBRT) was performed in all patients with cobalt 60 gamma rays or 4 MV photons from a linear accelerator. The total dose was 30-40 Gy with a median of 35 Gy in daily fractions of 2-3 Gy.
Outcomes: Overall survival (OS) prognostic factors for survival.
Follow up: -
Results: Survival (n=174): Median OS for RPA class I = 11.7 months Median OS for RPA class II = 6.2 months Median OS for RPA class III = 3 months Median OS for BS-BM class 3 = 24.6 months Median OS for BS-BM class 2 = 6.6 months Median OS for BS-BM class 1 = 4.7 months Median OS for BS-BM class 0 = 2.8 months

<p>Median OS for long term survivors (n=3) = 4.42 years (range: 3.8-5.1)</p> <p>1 year survival rate = 33.4% 2 year survival rate = 16.7% 3 years survival rate = 8.8%</p> <p>1 year survival rate for patients with RPA class I (n=28) = 55.6% 1 year survival rate for patients with RPA class II (n=39) = 37.7% 1 year survival rate for patients with RPA class III (n=75) = 21.7% (P < 0.0001)</p> <p>Prognostic factors for survival from univariate analysis: KPS (≥ 70 vs < 70) (P < 0.0001) Surgical resection vs no surgical resection (P < 0.0001) Single vs multiple brain metastases (P = 0.003) Control of primary disease vs not (P = 0.002) BS-BM score (P < 0.0001)</p> <p>Prognostic factors for survival from multivariate analysis: Surgical resection (P < 0.0001) Absence of extracranial metastases (P < 0.0001) RPA class I (P < 0.0001)</p>
<p>General comments: This paper describes the findings from a retrospective analysis of data from case files of patients with brain metastases secondary to breast cancer that had been treated with WBRT at a single institution between January 1996 and December 2004. 68 patients had a new diagnosis of brain metastases and 20 patients had local or locoregional relapse.</p> <p>Recursive partitioning analysis was used to classify patients with brain metastases into three classes on the basis of KPS, control of primary tumour and presence or otherwise of extracerebral metastases. 39 patients were RPA class I, 46 patients were class II and 89 patients were class III. 66 patients had single brain metastases and 108 had multiple metastases. Of these 174 patients, 81 had primary breast cancer and this report is confined to these patients.</p> <p>The authors concluded from these analyses that RPA class was the most significant indicator for survival and was a better indicator than BS-BM. RPA class I patients could be treated with local resection followed by WBRT, particularly if these patients had a single brain metastasis, higher performance status and controlled extracranial disease. Patients with RPA class III or BS-BM of 0, conversely, were not good candidates for this sequence of treatment whilst those of RPA class II or BS-BM of 1 were difficult to treat with certainty.</p> <p>This study was reasonably presented but, nonetheless, being a retrospective review was of less evidential value than a prospective comparative study.</p>

Rudnicka <i>et al.</i> (2007)
Design: Retrospective case series (therapy). Evidence level: 3 Country: Poland
Inclusion criteria: Patients with leptomeningeal metastases (LM) from breast cancer
Exclusion criteria: -
Population:

Number of patients = 67 Age range: 27 to 75 years. Median age = 49 years.
Interventions: Intrathecal methotrexate (MTX) at 10 mg per dose plus dexamethasone given twice a week until response and then once a week. Systemic chemotherapy with a variety of drugs including vinorelbine, 5'-fluorouracil, anthracycline, platinum, taxanes, etoposide, BCNU or temozolomide. WBRT or spinal cord radiotherapy at 30 Gy in 10 fractions or 20 Gy in 5 fractions A combined modality of all intrathecal MTX, systemic chemotherapy and irradiation.
Outcomes: Overall survival (OS) prognostic factors
Follow up:
Results: 57 patients had intrathecal MTX. Mean dosage was 7 courses (range: 1-15). 33 patients with bulky disease also had WBRT and 15 underwent LM radiotherapy. 10 patients were given spinal cord radiotherapy and 27 patients had a combined modality of all treatments. 41 patients had systemic chemotherapy, usually after completion of radiotherapy and/or after intrathecal treatment. 3/67 patients were given chemotherapy only. Survival (n=67): Response to treatment = 76% Median OS = 16 weeks Mean OS = 29 weeks Survival > 6 months = 22% Survival > 1 year = 7% Median OS for responders = 18 weeks Median OS for non-responders = 6 weeks. Prognostic factors for survival from univariate analysis: Systematic i.v. chemotherapy (P = 0.00009) Intrathecal chemotherapy (P = 0.008) WBRT (P = 0.004) Radiotherapy of LM did not influence survival Prognostic factors for survival from multivariate analysis: Systemic i.v. chemotherapy vs not (P < 0.001) HR = 3.101 (95%CI: 1.716-5.607) Intrathecal chemotherapy vs not (P = 0.001) HR = 3.268 (95%CI: 1.589-6.738) KPS < 60% vs ≥ 60% (P = 0.015) HR = 1.953 (95%CI: 1.136-3.359) Non-significant factors: Age ≤ 65 years vs age > 65 years WBRT RT of spinal LM Multimodal (intrathecal, i.v. chemotherapy and RT) treatment vs < 3 modalities Clinical response to treatment
General comments: This paper presents the findings from a retrospective review of case files from 67 patients treated for leptomeningeal metastases from breast cancer between 2000 and 2005 at two cancer centres.

16 patients had isolated LM and the remaining 51 patients also had more distant metastatic disease.

The authors concluded that chemotherapy appeared to be crucial in the multimodal treatment of LM and both intrathecal and i.v. chemotherapy improved patient survival. WBRT may have been shown in other studies to have improved quality of life but had a questionable effect on survival.

Health Economic Summary

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Appendix A – Search Strategies

NATIONAL COLLABORATING CENTRE FOR CANCER				
Advanced Breast Cancer Clinical Guideline				
Chapter 2 - Presentation and Diagnosis			Literature search summary	
Topic 1: Imaging investigations for assessing disease extent & monitoring response to treatment				
1. Literature search details				
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1757	159	13/10/06
<i>Premedline</i>	Nov 9, 2006	7	0	13/10/06
<i>Embase</i>	1980 -	1089	61	13/10/06
<i>Cochrane Library</i>	Issue 3, 2006	267	20	10/10/06
<i>Cinahl</i>	1982 -	33	0	13/10/06
<i>BNI</i>	1994 -	0	0	13/10/06
<i>Psychinfo</i>	1806 -	0	0	13/10/06
<i>Amed</i>	1985 -	1	0	13/10/06
<i>SIGLE</i>	1980 - 2005	0	0	10/10/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	2289	212	14/10/06
<i>Biomed Central</i>	1997 -	63	0	15/10/06
Total References retrieved (after de-duplication): 314				
Medline search strategy (<i>This search strategy is adapted to each database</i>)				
1 exp Breast Neoplasms/ 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ 3 Carcinoma, Intraductal, Noninfiltrating/ 4 Carcinoma, Lobular/ 5 Carcinoma, Medullary/ 6 exp mammary neoplasms/ 7 or/1-6 8 exp Breast/ 9 breast.tw. 10 8 or 9 11 (breast adj milk).tw. 12 (breast adj tender\$.tw. 13 11 or 12 14 10 not 13 15 exp Neoplasms/ 16 14 and 15 17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp. 18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp. 19 Paget's Disease, Mammary/ 20 (paget\$ and (breast\$ or mammary or nipple\$)).tw. 21 or/16-20 22 7 or 21				

23 exp Neoplasm Metastasis/
 24 ((breast\$ or mammar\$) adj5 (metastat\$ or advance\$ or second\$ or recurren\$ or inoperab\$ or disseminat\$ or incur\$)).mp.
 25 (breast\$ or mammar\$).mp.
 26 ((stage or grade or type) adj3 ("3" or "4" or c or d or iii\$ or iv\$)).mp.
 27 (N1 or N2\$ or N3\$ or pN1\$ or pN2\$ or pN3\$).mp.
 28 26 or 27
 29 25 and 28
 30 23 or 24 or 29
 31 22 and 30
 32 exp Radiography/
 33 (radiograph\$ or xray or x-ray).mp.
 34 exp Ultrasonography/
 35 (ultrasound\$ or ultrasonograph\$ or sonogra\$ or ultrasonic or echogra\$ or echotomogra\$).mp.
 36 exp Radionuclide Imaging/
 37 (radionuclide adj1 (scan\$ or imaging)).tw.
 38 scintigraph\$.mp.
 39 exp Magnetic Resonance Imaging/
 40 magnet\$ resonance.mp.
 41 (MRI or MRI\$1 or NMR\$1).tw.
 42 (MR adj (imag\$ or scan\$)).tw.
 43 (magnet\$ adj (imag\$ or scan\$)).tw.
 44 (magneti?ation adj3 imaging).tw.
 45 exp Tomography/
 46 exp Tomography, X-Ray Computed/
 47 PET\$1.tw.
 48 PET-CT.tw.
 49 (comput\$ adj1 tomogra\$).tw.
 50 ((diffusion or planar or echoplanar or functional or nuclear or radionuclide or radioisotope or conventional) adj2 (scan\$ or imag\$ or tomogra\$)).tw.
 51 (FDG-PET or FES-PET or 18F-FDG-PET or FLT-PET).mp.
 52 ((CT or CAT) adj (scan\$ or imaging or examination)).tw.
 53 (PET adj (scan\$ or imag\$ or examination)).tw.
 54 positron emission tomograph\$.mp.
 55 (bone adj3 (scan\$ or imag\$)).mp.
 56 or/32-55
 57 31 and 56
 58 Liver Neoplasms/
 59 Lung Neoplasms/
 60 Bone Neoplasms/
 61 ((liver or bone or hepatic or lung) adj metastases).mp.
 62 or/58-61
 63 22 and 56 and 62
 64 57 or 63

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	131	15/10/06
<i>Premedline</i>	1	15/10/06
<i>Embase</i>	237	15/10/06
<i>Cochrane Library (except NHSEED)</i>	69	15/10/06
<i>NHSEED</i>	24	15/10/06

<i>Cinahl</i>	19	15/10/06
<i>BNI</i>	0	15/10/06
<i>Psychinfo</i>	1	15/10/06
<i>AMED</i>	1	15/10/06
<i>EconLit</i>	0	15/10/06
<i>Web of Science (SCI & SSCI)</i>	90	15/10/06
<i>SIGLE</i>	0	15/10/06

Total References retrieved (after de-duplication): 479

3. Any further comments

Systematic reviews (2002+), RCT's & Observational filters applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	317	38	02/04/08
<i>Premedline (June 27, 2008)</i>	27	3 (already selected)	30/06/08
<i>Embase</i>	315	18	05/03/08
<i>Cochrane Library (Issue 1, 2008)</i>	62	2	21/02/08
<i>Cinahl</i>	30	4	19/03/08
<i>BNI</i>	0	0	21/02/08
<i>Psychinfo</i>	0	0	21/02/08
<i>AMED</i>	1	0	21/02/08
<i>Web of Science (SCI & SSCI)</i>	621	38	28/03/08

Total References retrieved (after de-duplication): 65

Plus 1 additional reference picked up from search alerts until 1st July 2008. Final Total: 66

Topic 2: Pathological assessment and reassessment on tumour samples**1. Literature search details**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1752	54	18/12/06
<i>Premedline</i>	Dec 18, 2006	23	1	07/12/06
<i>Embase</i>	1980 -	1394	23	18/12/06
<i>Cochrane Library</i>	Issue 4, 2006	423	11	07/12/06
<i>Cinahl</i>	1982 -	88	2	07/12/06
<i>BNI</i>	1994 -	0	0	07/12/06
<i>Psychinfo</i>	1806 – Dec Wk2	4	0	07/12/06
<i>Amed</i>	1985 -	0	0	07/12/06
<i>SIGLE</i>	1980 - 2005	0	0	19/12/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	1331	47	19/12/06
<i>Biomed Central</i>	1997 -	106	0	19/12/06

Total References retrieved (after de-duplication): 103

Medline search strategy (*This search strategy is adapted to each database*)

- 1 exp Breast Neoplasms/
- 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
- 3 Carcinoma, Intraductal, Noninfiltrating/
- 4 Carcinoma, Lobular/
- 5 Carcinoma, Medullary/
- 6 exp mammary neoplasms/
- 7 or/1-6

8 exp Breast/
9 breast.tw.
10 8 or 9
11 (breast adj milk).tw.
12 (breast adj tender\$.tw.
13 11 or 12
14 10 not 13
15 exp Neoplasms/
16 14 and 15
17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
19 Paget's Disease, Mammary/
20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
21 or/16-20
22 7 or 21
23 Receptor, erbB-2/
24 Genes, erbB-2/
25 (HER2 or HER-2 or c-erbB2 or human epidermal growth factor receptor\$.mp.
26 Receptors, Estrogen/
27 ((oestrogen\$ or estrogen or EgR or ER) adj3 (status or test\$ or level\$ or receptor\$ or expression)).mp.
28 ((ER adj2 positiv\$) or (ER adj2 negativ\$) or (EgR adj2 positiv\$) or (EgR adj2 negativ\$) or (oestrogen\$ adj2 positiv\$) or (oestrogen\$ adj2 negativ\$) or (estrogen adj2 negativ\$) or (estrogen adj2 positiv\$)).mp.
29 Receptors, Progesterone/
30 ((progesteron\$ or progestin or PgR or PR) adj3 (status or test\$ or level\$ or receptor\$ or expression)).mp.
31 ((PR adj2 positiv\$) or (PR adj2 negativ\$) or (PgR adj2 positiv\$) or (PgR adj2 negativ\$) or (progesteron\$ adj2 positiv\$) or (progesteron\$ adj2 negativ\$) or (progestin adj2 negativ\$) or (progestin adj2 positiv\$)).mp.
32 or/23-31
33 22 and 32
34 ((change or alter or acquire\$ or alter\$ or conserve\$ or lost or unchange\$ or revert\$) adj2 (status or express\$)).mp.
35 ((concordan\$ or discordan\$) adj5 (status or express\$)).mp.
36 34 or 35
37 33 and 36
38 ((primary or primitive) adj (tumo?r or disease or breast cancer or invasive breast cancer or focuses or diagnosis or lesion\$)).mp.
39 33 and 38
40 Disease Progression/
41 (tumo?r progress\$ or cancer progress\$ or disease progress\$ or breast cancer progress\$).mp.
42 40 or 41
43 33 and 42
44 (distant metastases or local recurren\$ or minimal residual disease).mp.
45 ((metastatic or recurrent) adj (disease\$ or focuses or site\$ or lesion\$ or breast cancer or tissue\$ or disease\$ or tumo?r)).mp.
46 44 or 45
47 33 and 46
48 37 or 39 or 43 or 47

2. Any further comments

Systematic reviews (2002+), RCT's & Observational filters applied to basic search for the clinical review. Not animal or laboratory studies, only clinical studies chosen. Health economics search not required.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	401	3	05/03/08
<i>Premedline (June 27, 2008)</i>	44	1 (already selected)	30/06/08
<i>Embase</i>	391	3	05/03/08
<i>Cochrane Library (Issue 1, 2008)</i>	63	0	21/02/08
<i>Cinahl</i>	55	0	05/03/08
<i>BNI</i>	0	0	21/02/08
<i>Psychinfo</i>	3	0	21/02/08
<i>AMED</i>	0	0	21/02/08
<i>Web of Science (SCI & SSCI)</i>	318	6	05/03/08

Total References retrieved (after de-duplication): 9

Plus 1 additional reference picked up from search alerts until 1st July 2008. Final Total: 10

NATIONAL COLLABORATING CENTRE FOR CANCER

Advanced Breast Cancer Clinical Guideline

Chapter 3 - Information and Support

Literature search summary

Topic 23a & b: In patients who have to make decisions about the management of their disease, do decision support methods produce better QoL and improve outcomes

1. Literature search details

Part a.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2001 onwards	349	22	18/10/06
<i>Premedline</i>	2001 onwards	2	0	18/10/06
<i>Embase</i>	2001 onwards	471	36	18/10/06
<i>Cochrane Library</i>	2001 onwards	517	26	10/11/06
<i>Cinahl</i>	2001 onwards	104	21	10/11/06
<i>BNI</i>	2001 onwards	4	3	10/11/06
<i>Psychinfo</i>	2001 onwards	152	40	10/11/06
<i>SIGLE</i>	2001 - 2005	15	2	10/11/06
<i>Web of Science (SCI & SSCI)</i>	2001 onwards	362	60	10/11/06
<i>Biomed Central</i>	2001 onwards	17	4	10/11/06

Total References retrieved (after de-duplication): 147

Part b.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2001 onwards	172	58	21/12/06
<i>Premedline</i>	2001 onwards	1	1	21/12/06
<i>Embase</i>	2001 onwards	60	14	21/12/06
<i>Cochrane Library</i>	2001 onwards	45	0	21/12/06
<i>Cinahl</i>	2001 onwards	24	10	21/12/06
<i>BNI</i>	2001 onwards	4	0	21/12/06
<i>Psychinfo</i>	2001 onwards	9	6	21/12/06
<i>SIGLE</i>	2001 - 2005	12	0	21/12/06
<i>Web of Science (SCI & SSCI)</i>	2001 onwards	159	12	21/12/06
<i>Biomed Central</i>	2001 onwards	48	0	21/12/06

Total References retrieved (after de-duplication): 90

Medline search strategy (*This search strategy is adapted to each database*)

1. exp Breast Neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. exp breast/
4. exp neoplasms/
5. 3 and 4
6. (breast\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or dcis or ductal or infiltrat\$ or intraductal\$ or lobular or medullary)).mp.
7. exp mammary neoplasms/
8. (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or dcis or

ductal or infiltrat\$ or intraductal\$ or lobular or medullary)).mp.

9. or/1-2,5-8

Part a.

10. choice behavior/

11. decision making/

12. exp decision support techniques/

13. ((patient\$ or consumer\$) adj3 (decision\$ or choice or preference or participation)).tw.

14. ((personal or interpersonal or individual) adj3 (decision\$ or choice or preference\$ or participat\$)).tw.

15. (wom#n adj3 (decision\$ or choice or preference or participation)).tw.

16. (decision\$ adj3 (aid\$ or support\$)).tw.

17. exp Patient Participation/

18. Pamphlets/

19. exp Audiovisual Aids/

20. (video\$ or dvd\$).tw.

21. exp Internet/

22. exp Self-Help Groups/

23. (support\$ adj2 (group\$ or meet\$)).tw.

24. exp Patient Education/mt [Methods]

25. ((inform\$ or support\$) adj2 (tool\$ or method\$ or group\$)).tw.

26. or/10-25

27. 9 and 26

Part b.

10. choice behavior/

11. decision making/

12. exp decision support techniques/

13. ((patient\$ or consumer\$) adj3 (decision\$ or choice or preference or participation)).tw.

14. ((personal or interpersonal or individual) adj3 (decision\$ or choice or preference\$ or participat\$)).tw.

15. (wom#n adj3 (decision\$ or choice or preference or participation)).tw.

16. (decision\$ adj3 (aid\$ or support\$)).tw.

17 or/10-16

18. exp Patient Participation/

19. Pamphlets/

20. exp Audiovisual Aids/

21. (video\$ or dvd\$).tw.

22. exp Internet/

23. exp Self-Help Groups/

24. (support\$ adj2 (group\$ or meet\$)).tw.

25. exp Patient Education/mt [Methods]

26 ((inform\$ or support\$) adj2 (tool\$ or method\$ or group\$)).tw.

27 or/18-26

27. 9 and 17 and 27

2. Health Economics Literature search details

Part a.

Database name	No of references found	Finish date of search
<i>Medline</i>	129	07/11/06
<i>Premedline</i>	0	18/10/06
<i>Embase</i>	178	07/11/06
<i>Cochrane Library (except NHSEED)</i>	41	10/11/06
<i>NHSEED</i>	35	10/11/06
<i>Cinahl</i>	98	10/11/06
<i>BNI</i>	0	10/11/06

<i>Psychinfo</i>	14	10/11/06
<i>EconLit</i>	14	10/11/06
<i>Web of Science (SCI & SSCI)</i>	107	10/11/06
<i>SIGLE</i>	0	10/11/06

Total References retrieved (after de-duplication): 515

Part b.

Database name	No of references found	Finish date of search
<i>Medline</i>	37	21/12/06
<i>Premedline</i>	3	21/12/06
<i>Embase</i>	10	21/12/06
<i>Cochrane Library (except NHSEED)</i>	29	21/12/06
<i>NHSEED</i>	2	21/12/06
<i>Cinahl</i>	20	21/12/06
<i>BNI</i>	0	21/12/06
<i>Psychinfo</i>	0	21/12/06
<i>EconLit</i>	3	21/12/06
<i>Web of Science (SCI & SSCI)</i>	74	21/12/06
<i>SIGLE</i>	0	21/12/06

Total References retrieved (after de-duplication): 171

3. Any further comments

The following Cochrane Systematic Review was used as a basis: ***Decision aids for people facing health treatment or screening decisions (O'Connor et al) 2003***. This review last searched for evidence in mid 2001, so this search was undertaken from 2001 onwards. The search strategy was taken from the review and criteria for executing it followed accordingly. As there was very little evidence ALL stages of breast cancer were selected. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review. No date limit was placed on this search as original Cochrane Review did not cover cost-effectiveness.

4. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2006-2008 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	146 (182)	19 (20)	12/03/08 (30/06/08)
<i>Premedline (June 27, 2008)</i>	8	0	30/06/08
<i>Embase</i>	140	10	06/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	171	14	07/05/08 (30/06/08)
<i>Cinahl</i>	29	6	13/03/08
<i>BNI</i>	0	0	13/03/08
<i>Psychinfo</i>	6	1	13/03/08
<i>Web of Science (SCI & SSCI)</i>	232	18	07/05/08

Total References retrieved (after de-duplication): 35

Plus 1 additional reference picked up from search alerts until 1st July 2008. Final Total: 36

NATIONAL COLLABORATING CENTRE FOR CANCER

Advanced Breast Cancer Clinical Guideline

Chapter 4 - Systemic Disease

Literature search summary

Topic 4: The choice of first line treatment for patients with metastatic breast cancer: a) Endocrine Therapy b) Chemotherapy

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2006 onwards	304	1	11/07/07
<i>Premedline</i>	2006 onwards	68	0	11/07/07
<i>Embase</i>	2006 onwards	324	1	11/07/07
<i>Cochrane Library</i>	2006 onwards	93	1	11/07/07
<i>Cinahl</i>	2006 onwards	30	1	11/07/07
<i>BNI</i>	2006 onwards	0	0	11/07/07
<i>Psychinfo</i>	2006 onwards	2	0	11/07/07
<i>AMED</i>	2006 onwards	3	0	11/07/07
<i>SIGLE</i>	Not searched: database ended 2005			
<i>Web of Science (SCI & SSCI)</i>	2006 onwards	328	1	11/07/07
<i>Biomed Central</i>	2006 onwards	22	0	11/07/07

Total References retrieved (after de-duplication): 2

Medline search strategy (*This search strategy is adapted to each database*)

- 1 ((advanced or recurrent or metastatic or disseminated) adj2 breast cancer).ti,ab.
- 2 ((advanced cancer or recurrent cancer or metastatic cancer or disseminated cancer or advanced carcinoma or recurrent carcinoma or metastatic carcinoma or disseminated carcinoma) adj3 breast).ti,ab.
- 3 ((endocrin\$ or cytotox\$ or antiestrogen\$ or hormon\$ or antimetabolit\$) adj3 (treatment or therap\$ or agent\$ or chemotherap\$)).ti,ab.
- 4 (combined modality adj (therap\$ or treatment)).ti,ab.
- 5 systemic therap\$.ti,ab.
- 6 chemotherap\$.ti,ab.
- 7 chemo-endocrine.ti,ab.
- 8 megestrol acetate.ti.
- 9 medroxyprogesterone acetate.ti.
- 10 mitoxantron\$.ti.
- 11 mitozantron\$.ti.
- 12 adriamycin.ti.
- 13 doxorubicin.ti.
- 14 cyclophosphamid\$.ti.
- 15 fluorourac\$.ti.
- 16 methotrexat\$.ti.
- 17 1 or 2
- 18 or/3-16
- 19 17 and 18

2. Any further comments

The following Cochrane Systematic Review was used as a basis: *Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer (Wilcken et al) 2007*. This review last searched for evidence in August 2006, so

this search was undertaken from 2006 onwards. The basic search strategy was based on the focused strategy used in the review. A general exclusions filter only was used as limited data available. Health economics search not required.

3. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2007-2008 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	201	1	05/03/08
<i>Premedline (June 27, 2008)</i>	36	0	30/06/08
<i>Embase</i>	232	2	05/03/08
<i>Cochrane Library</i>	51	0	05/03/08
<i>Cinahl</i>	41	0	05/03/08
<i>BNI</i>	2	0	05/03/08
<i>Psychinfo</i>	4	0	05/03/08
<i>AMED</i>	3	0	05/03/08
<i>Web of Science (SCI & SSCI)</i>	308 (294)	1	05/03/08

Total References retrieved (after de-duplication): 2

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 2

Topic 8: In patients with metastatic breast cancer which hormone treatments are active and in patients with metastatic breast cancer which hormone treatment is most active. Pt1 (AI's)

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2003 onwards	286	59	23/01/07
<i>Premedline</i>	2003 onwards	29	3	23/01/07
<i>Embase</i>	2003 onwards	773	64	24/01/07
<i>Cochrane Library</i>	2003 onwards	82	48	25/01/07
<i>Cinahl</i>	2003 onwards	52	0	23/01/07
<i>BNI</i>	2003 onwards	0	0	23/01/07
<i>Psychinfo</i>	2003 onwards	2	1	23/01/07
<i>AMED</i>	2003 onwards	4	0	23/01/07
<i>SIGLE</i>	2003 - 2005	0	0	23/01/07
<i>Web of Science (SCI & SSCI)</i>	2003 onwards	419	98	25/01/07
<i>Biomed Central</i>	2003 onwards	86	0	24/01/07

Total References retrieved (after de-duplication): 140

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
- 3 Carcinoma, Intraductal, Noninfiltrating/
- 4 Carcinoma, Lobular/
- 5 Carcinoma, Medullary/
- 6 exp mammary neoplasms/
- 7 or/1-6
- 8 exp Breast/
- 9 breast.tw.
- 10 8 or 9

11 (breast adj milk).tw.
 12 (breast adj tender\$.tw.
 13 11 or 12
 14 10 not 13
 15 exp Neoplasms/
 16 14 and 15
 17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 18 (mammary\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 19 Paget's Disease, Mammary/
 20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 21 or/17-20
 22 7 or 21
 23 exp Neoplasm Metastasis/
 24 ((breast\$ or mammary\$) adj5 (metastat\$ or advance\$ or second\$ or recurrent\$ or inoperab\$ or disseminat\$ or incur\$)).mp.
 25 (breast\$ or mammary\$).mp.
 26 ((stage or grade or type) adj3 ("3" or "4" or c or d or iii\$ or iv\$)).mp.
 27 (N1 or N2\$ or N3\$ or pN1\$ or pN2\$ or pN3\$).mp.
 28 26 or 27
 29 25 and 28
 30 23 or 24 or 29
 31 22 and 30
 32 exp Aromatase Inhibitors/
 33 (arimidex or aromasin or femara).af.
 34 (anastrozole or exemestane or letrozole).mp.
 35 Megestrol Acetate/
 36 megestrol acetat\$.mp.
 37 Aminoglutethimide/
 38 Aminoglutethimid\$.mp.
 39 or/32-38
 40 31 and 39

2. Health Economics Literature search details

See next search for details

3. Any further comments

The following Cancer Care Ontario Practice Guideline was used as a basis: ***The role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer (Breast Cancer Disease Site Group) 2003.*** This review last searched for evidence in October 2003, so this search was undertaken from 2003 onwards. No filters were placed on the results, but only trials and good quality reviews were included. The following Cochrane Review (identified during searching) formed a large part of the evidence review: ***Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women (Gibson et al) 2007.***

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	152	12	10/03/08
Premedline (June 27, 2008)	44	4 (already selected)	30/06/08
Embase	508	13	10/03/08

Cochrane Library	29	3	10/03/08
Cinahl	46	2	10/03/08
BNI	0	0	10/03/08
Psychinfo	2	0	10/03/08
AMED	0	0	10/03/08
Web of Science (SCI & SSCI)	209	13	11/03/08

Total References retrieved (after de-duplication): 25

Plus additional references picked up from search alerts until 1st July 2008 & combined with pt2 of Topic 8 search. Final Total: 56

Topic 8: In patients with metastatic breast cancer which hormone treatments are active and in patients with metastatic breast cancer which hormone treatment is most active. Pt2 (Remaining Treatments)

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1990 onwards	1506	254	26/04/07
Premedline	1990 onwards	13	0	26/04/07
Embase	1990 onwards	1089	108	27/04/07
Cochrane Library	1990 onwards	1181	137	27/04/07
Cinahl	1990 onwards	140	3	26/04/07
AMED	1990 onwards	4	0	26/04/07
BNI	1990 onwards	1	0	26/04/07
Psychinfo	1990 onwards	7	1	26/04/07
SIGLE	1990 – 2005	14	0	26/04/07
Web of Science (SCI & SSCI)	1990 onwards	2208	140	01/05/07
Biomed Central	1990 onwards	53	0	01/05/07

Total References retrieved (after de-duplication): 393

Medline search strategy (*This search strategy is adapted to each database*)

1 exp Breast Neoplasms/

2 exp "Neoplasms, Ductal, Lobular, and Medullary"/

3 Carcinoma, Intraductal, Noninfiltrating/

4 Carcinoma, Lobular/

5 Carcinoma, Medullary/

6 exp mammary neoplasms/

7 or/1-6

8 exp Breast/

9 breast.tw.

10 8 or 9

11 (breast adj milk).tw.

12 (breast adj tender\$.tw.

13 11 or 12

14 10 not 13

15 exp Neoplasms/

16 14 and 15

17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.

18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 19 Paget's Disease, Mammary/
 20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 21 or/17-20
 22 7 or 21
 23 exp Neoplasm Metastasis/
 24 ((breast\$ or mammar\$) adj5 (metastat\$ or advance\$ or second\$ or recurren\$ or inoperab\$ or disseminat\$ or incur\$)).mp.
 25 (breast\$ or mammar\$).mp.
 26 ((stage or grade or type) adj3 ("3" or "4" or c or d or iii\$ or iv\$)).mp.
 27 (N1 or N2\$ or N3\$ or pN1\$ or pN2\$ or pN3\$).mp.
 28 26 or 27
 29 25 and 28
 30 23 or 24 or 29
 31 22 and 30
 32 Tamoxifen/
 33 (Nolvadex or tamoxifen\$).mp.
 34 10540-29-1.rn.
 35 (fulvestrant or faslodex).mp.
 36 ICI 182780.mp.
 37 Diethylstilbestrol/
 38 (diethylstilbestrol or stilboestrol).mp.
 39 exp Testosterone/
 40 (testosterone or striant).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 41 Dihydrotestosterone/
 42 (trilostane or modrenal or dihydrotestosterone).mp.
 43 exp Medroxyprogesterone/
 44 Megestrol Acetate/
 45 (megestrol acetat\$ or megace).mp.
 46 medroxyprogesterone acetat\$.mp.
 48 Goserelin/
 49 (goserelin\$ or zoladex).mp.
 50 Triptorelin/
 51 (triptorelin or decapeptyl).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 52 Ovariectomy/
 53 (oopherectom\$ or ovariectom\$ or female castrat\$).mp.
 54 irradiation menopause.mp.
 55 or/32-54
 56 31 and 55

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	56	01/05/07
<i>Premedline</i>	4	01/05/07
<i>Embase</i>	254	01/05/07
<i>Cochrane Library (except NHSEED)</i>	101	04/05/07
<i>NHSEED</i>	27	04/05/07
<i>Cinahl</i>	61	01/05/07
<i>Psychinfo</i>	1	01/05/07
<i>Amed, BNI</i>	0 in each	01/05/07
<i>EconLit</i>	4	01/05/07

Web of Science (SCI & SSCI)	103	01/05/07
SIGLE	0	01/05/07

Total References retrieved (after de-duplication): 499

3. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. A decision was made in consultation with the GDG that we would limit the search 1990 onwards as the amount of data available was huge and also that more recent data would be required. The health economics search was for both parts of Topic 8, with no date limit as possible limited health economics data available and the AIs reviews did not cover cost-effectiveness. Therefore, the clinical search string detailed above was added to clinical search string used for pt 1, and then a SIGN Health Economics filter & SCHARR Quality of Life filter were applied to the combined basic search.

4. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	208	12	28/04/08
<i>Premedline (June 27, 2008)</i>	31	4 (already selected)	30/06/08
<i>Embase</i>	525	10	29/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	89	5	28/04/08
<i>Cinahl</i>	68	5	29/04/08
<i>BNI</i>	1	0	28/04/08
<i>Psychinfo</i>	5	0	28/04/08
<i>AMED</i>	1	0	28/04/08
<i>Web of Science (SCI & SSCI)</i>	462	27	29/04/08

Total References retrieved (after de-duplication): 32

Plus additional references picked up from search alerts until 1st July 2008 & combined with pt1 of Topic 8 search. Final Total: 56

5. Additional Search

An additional search was undertaken to ensure that the evidence for male breast cancer patients was specifically looked at in terms of hormonal therapy as it may differ from the hormonal treatment given to female breast cancer patients. The basic search strategies for parts 1 and 2 of this topic were used as the basic search.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	199	69	30/05/08
<i>Premedline (July 1, 2008)</i>	2	0	01/07/08
<i>Embase</i>	223	67	30/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	41	8	30/05/08
<i>Cinahl</i>	37	4	30/05/08
<i>BNI</i>	0	0	30/05/08
<i>Psychinfo</i>	1	0	30/05/08
<i>AMED</i>	0	0	30/05/08
<i>Web of Science (SCI & SSCI)</i>	75	21	30/05/08

Total References retrieved (after de-duplication): 120

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 120

Topic 10a & b: Combination chemotherapy versus a. sequential chemotherapy or b. single chemotherapy (specifically for part b. eight single drugs: Docetaxel, Paclitaxel, Vinorelbine, Capecitabine, Gemcitabine, Epirubicin, Doxorubicin, Carboplatin as per PICO table)

1. Literature search details

Part a.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	678	30	23/04/07
<i>Premedline</i>	Apr 25, 2007	3	0	23/04/07
<i>Embase</i>	1980 -	1,247	23	24/04/07
<i>Cochrane Library</i>	Issue 2, 2007	1,125	35	25/04/07
<i>Cinahl</i>	1982 -	38	2	23/04/07
<i>BNI</i>	1994 -	0	0	23/04/07
<i>Psychinfo</i>	1806 -	4	0	23/04/07
<i>Amed</i>	1985 -	1	0	23/04/07
<i>SIGLE</i>	1980 - 2005	0	0	23/04/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	995	39	24/04/07
<i>Biomed Central</i>	1997 -	141	0	24/04/07

Total References retrieved (after de-duplication): 74

Part b.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	852	25	26/09/07
<i>Premedline</i>	Sept 25, 2007	88 (no filters)	1	26/09/07
<i>Embase</i>	1980 -	1296	30	02/10/07
<i>Cochrane Library</i>	Issue 3, 2007	327	41	28/09/07
<i>Cinahl</i>	1982 -	94	5	26/09/07
<i>BNI</i>	1994 -	1 (no filters)	0	26/09/07
<i>Psychinfo</i>	1806 -	1 (no filters)	0	26/09/07
<i>Amed</i>	1985 -	3 (no filters)	0	26/09/07
<i>SIGLE</i>	1980 - 2005	8	0	26/09/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	1894/1351 (1299)	55	03/10/07
<i>Biomed Central</i>	1997 -	76	0	26/09/07

Total References retrieved (after de-duplication): 82

Medline search strategy (*This search strategy is adapted to each database*)

- 1 exp Breast Neoplasms/
- 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
- 3 Carcinoma, Intraductal, Noninfiltrating/
- 4 Carcinoma, Lobular/
- 5 Carcinoma, Medullary/
- 6 exp mammary neoplasms/
- 7 or/1-6
- 8 exp Breast/
- 9 breast.tw.
- 10 8 or 9
- 11 (breast adj milk).tw.
- 12 (breast adj tender\$.tw.
- 13 11 or 12

14 10 not 13
15 exp Neoplasms/
16 14 and 15
17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
19 Paget's Disease, Mammary/
20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
21 or/16-20
22 7 or 21
23 exp Neoplasm Metastasis/
24 ((breast\$ or mammar\$) adj5 (metastat\$ or advance\$ or second\$ or recurren\$ or inoperab\$ or disseminat\$ or incur\$)).mp.
25 (breast\$ or mammar\$).mp.
26 ((stage or grade or type) adj3 ("3" or "4" or c or d or iii\$ or iv\$)).mp.
27 (N1 or N2\$ or N3\$ or pN1\$ or pN2\$ or pN3\$).mp.
28 26 or 27
29 25 and 28
30 23 or 24 or 29
31 22 and 30
Part a.
32 (multiple-agent\$ or multiple agent\$ or multiple-drug\$ or multiple drug\$ or combination\$ or combined with or concomitant or polychemotherap\$ or concurrent).mp.
33 (separate or sequential\$ or consecutive or successive or following).mp.
34 31 and 32 and 33
35 (single-agent or single agent or single-drug or single drug or monotherap\$ or monochemotherap\$).mp.
36 31 and 32 and 35
37 34 or 36
Part b.
32 (docetaxel\$ or taxotere\$).mp.
33 Paclitaxel/
34 (paclitaxel\$ or taxol\$ or onxol\$).mp.
35 (vinorelbina\$ or navelbin\$).mp.
36 (capecitabine\$ or xeloda).mp.
37 (gemcitabine\$ or gemzar\$).mp.
38 exp Epirubicin/
39 (epirubicin\$ or ellence).mp.
40 exp Doxorubicin/
41 (adriamycin\$ or doxorubicin\$ or doxil or rubex).mp.
42 exp Carboplatin/
43 (carboplatin\$ or paraplatain\$).mp.
44 114977-28-5.rn.
45 33069-62-4.rn.
46 71486-22-1.rn.
47 154361-50-9.rn.
48 103882-84-4.rn.
49 56420-45-2.rn.
50 23214-92-8.rn.
51 41575-94-4.rn.
52 or/1-20
53 31 and 52

2. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. Health economics search not required.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only. The searches for parts a and b were executed together.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	353	5	06/05/08
<i>Premedline (June 27, 2008)</i>	34	1	30/06/08
<i>Embase</i>	476	5	07/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	212	5	07/05/08
<i>Cinahl</i>	76	3	07/05/08
<i>BNI</i>	0	0	06/05/08
<i>Psychinfo</i>	1	0	06/05/08
<i>AMED</i>	0	0	06/05/08
<i>Web of Science (SCI & SSCI)</i>	637	8	07/05/08

Total References retrieved (after de-duplication): 14

0 additional references picked up from search alerts until 1st July 2008. Final Total: 14

Topic 5: The clinical effectiveness and cost effectiveness of vinorelbine for breast cancer**1. Literature search details**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2000 onwards	283	105	27/10/06
<i>Premedline</i>	2000 onwards	13	6	27/10/06
<i>Embase</i>	2000 onwards	833	117	27/10/06
<i>Cochrane Library</i>	2000 onwards	67	37	30/10/06
<i>Cinahl</i>	2000 onwards	22	6	27/10/06
<i>BNI</i>	2000 onwards	0	0	27/10/06
<i>Psychinfo</i>	2000 onwards	0	0	27/10/06
<i>Amed</i>	2000 onwards	1	1	27/10/06
<i>SIGLE</i>	2000 - 2005	5	0	27/10/06
<i>Web of Science (SCI & SSCI)</i>	2000 onwards	532	207	30/10/06
<i>Biomed Central</i>	2000 onwards	53	2	30/10/06

Total References retrieved (after de-duplication): 254

Medline search strategy (*This search strategy is adapted to each database*)

- 1 vinorelbine.ti,ab,nm
- 2 navelbine.ti,ab
- 3 1 or 2
- 4 exp Breast Neoplasms/all subheadings
- 5 (breast\$ adj4 (cancer\$ or tum?r or malignant\$)).ti,ab
- 6 (breast\$ adj4 (oncolog\$ or carcinoma\$)).ti,ab
- 7 or/4-6
- 8 3 and 7

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	13	27/10/06
<i>Premedline</i>	0	27/10/06
<i>Embase</i>	84	27/10/06
<i>Cochrane Library (except NHSEED)</i>	18	30/10/06
<i>NHSEED</i>	5	30/10/06
<i>Cinahl</i>	2	27/10/06
<i>BNI, Psychinfo, Amed</i>	0 in each	27/10/06
<i>EconLit</i>	0	27/10/06
<i>Web of Science (SCI & SSCI)</i>	15	30/10/06
<i>SIGLE</i>	0	27/10/06

Total References retrieved (after de-duplication): 106

3. Any further comments

This search constituted an update of an HTA report, details as below: ***The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: systematic review and economic evaluation (Lewis et al) July 2002***. This review last searched for evidence in June 2000, so this search was undertaken from 2000 onwards. The search strategy was taken from the review and criteria for executing it followed accordingly. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	90	17	05/03/08
<i>Premedline (June 27, 2008)</i>	28	7 (already selected) + 1	30/06/08
<i>Embase</i>	221	20	05/03/08
<i>Cochrane Library (Issue 1, 2008)</i>	19	7	26/02/08
<i>Cinahl</i>	10	3	05/03/08
<i>BNI</i>	0	0	26/02/08
<i>Psychinfo</i>	0	0	26/02/08
<i>AMED</i>	0	0	26/02/08
<i>Web of Science (SCI & SSCI)</i>	199	39	05/03/08

Total References retrieved (after de-duplication): 45

4 additional references picked up from search alerts until 1st July 2008. Final Total: 49

Topic 6: The clinical effectiveness and cost effectiveness of capecitabine for breast cancer

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2002 onwards	114	48	02/03/06
<i>Premedline</i>	2002 onwards	2	1	02/03/06
<i>Embase</i>	2002 onwards	440	62	02/03/06
<i>Cochrane Library</i>	2002 onwards	31	16	02/03/06
<i>Cinahl</i>	2002 onwards	11	5	02/03/06
<i>BNI</i>	2002 onwards	1	0	02/03/06
<i>Psychinfo</i>	2002 onwards	0	0	02/03/06
<i>Amed</i>	2002 onwards	0	0	02/03/06
<i>SIGLE</i>	2002 - 2005	1	1	02/03/06
<i>Web of Science (SCI & SSCI)</i>	2002 onwards	318	78	02/03/06
<i>Biomed Central</i>	2002 onwards	44	0	02/03/06

Total References retrieved (after de-duplication): 125

Medline search strategy (This search strategy is adapted to each database)

- 1 capecitabine.mp
- 2 xeloda.mp
- 3 1 or 2
- 4 exp Breast Neoplasms/
- 5 (breast\$ adj4 (cancer\$ or tum?r or malignanc\$)).mp
- 6 (breast\$ adj4 (oncolog\$ or carcinoma\$ or neoplas\$)).mp
- 7 or/4-6
- 8 3 and 7

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	10	15/03/06
<i>Premedline</i>	0	15/03/06
<i>Embase</i>	61	15/03/06
<i>Cochrane Library (except NHSEED)</i>	11	15/03/06
<i>NHSEED</i>	2	15/03/06
<i>Cinahl</i>	4	15/03/06
<i>BNI, Psychinfo, Amed</i>	0 in each	15/03/06
<i>EconLit</i>	0	15/03/06
<i>Web of Science (SCI & SSCI)</i>	11	15/03/06
<i>SIGLE</i>	0	15/03/06

Total References retrieved (after de-duplication): 75

3. Any further comments

This search constituted an update of an HTA report, details as below: ***Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda) for locally advanced and/or metastatic breast cancer (Jones et al) Feb 2004.*** This review last searched for evidence in May 2002, so this search was undertaken from 2002 onwards. The search strategy was taken from the review and criteria for executing it followed accordingly. Only capecitabine monotherapy or capecitabine/docetaxel were considered, all other combinations were sifted out (as per HTA exclusion criteria). SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2005-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	99	49	05/03/08
<i>Premedline (June 27, 2008)</i>	7	1	30/06/08
<i>Embase</i>	97	39	05/03/08
<i>Cochrane Library (Issue 1, 2008)</i>	38	14	27/02/08
<i>Cinahl</i>	20	9	05/03/08
<i>BNI</i>	1	0	27/02/08
<i>Psychinfo</i>	0	0	27/02/08
<i>AMED</i>	0	0	27/02/08
<i>Web of Science (SCI & SSCI)</i>	266	79	05/03/08

Total References retrieved (after de-duplication): 109

Plus 4 additional references picked up from search alerts until 1st July 2008. Final Total: 113

Topic 7: The clinical effectiveness and cost effectiveness of taxanes for breast cancer**1. (a) Main literature search details**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2000 onwards	1196 (with filters)	382	23/02/07

Premedline	2000 onwards	13	3	21/02/07
Embase	2000 onwards	975	308	23/02/07
Cochrane Library	2000 onwards	440	165	26/02/07
Cinahl	2000 onwards	105 (with filters)	28	21/02/07
BNI	2000 onwards	3	0	21/02/07
Psychinfo	2000 onwards	3	0	21/02/07
Amed	2000 onwards	8	1	21/02/07
SIGLE	2000 - 2005	0	0	21/02/07
Web of Science (SCI & SSCI)	2000 onwards	1,348	392	01/03/07
Biomed Central	2000 onwards	92	2	21/02/07

Total References retrieved (after de-duplication): 625

(b) Supplementary literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	66	13	31/10/07
Premedline	Oct 30, 2007	3	0	31/10/07
Embase	1980 -	58	18	31/10/07
Cochrane Library	Issue 4, 2007	19	6	31/10/07
Cinahl	1982 -	4	2	31/10/07
BNI	1994 -	0	0	31/10/07
Psychinfo	1806 -	0	0	31/10/07
Amed	1985 -	0	0	31/10/07
SIGLE	1980 - 2005	0	0	31/10/07
Web of Science (SCI & SSCI)	1970 -	175	34	31/10/07
Biomed Central	1997 -	16	0	31/10/07

Total References retrieved (after de-duplication): 37

Medline search strategy (*This search strategy is adapted to each database*)

- 1 Paclitaxel/ [all subheadings]
- 2 paclitaxel* or docetaxel*
- 3 taxol* or taxotere*
- 4 taxanes
- 5 or/1-4
- 6 exp Breast Neoplasms/all subheadings
- 7 (breast\$ adj4 (cancer\$ or tum?* or malignant\$)).ti,ab
- 8 (breast\$ adj4 (oncolog\$ or carcinoma\$)).ti,ab
- 9 or/6-8
- 10 5 and 9

(b) Supplementary literature search details

- 1 exp Breast Neoplasms/
- 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
- 3 Carcinoma, Intraductal, Noninfiltrating/
- 4 Carcinoma, Lobular/
- 5 Carcinoma, Medullary/
- 6 exp mammary neoplasms/
- 7 or/1-6
- 8 exp Breast/
- 9 breast.tw.
- 10 8 or 9
- 11 (breast adj milk).tw.

12 (breast adj tender\$.tw.
 13 11 or 12
 14 10 not 13
 15 exp Neoplasms/
 16 14 and 15
 17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 19 Paget's Disease, Mammary/
 20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 21 or/17-20
 22 7 or 21
 23 (docetaxel\$ or taxotere\$).mp.
 24 114977-28-5.rn.
 25 (gemcitabin\$ or gemzar).mp.
 26 103882-84-4.rn.
 27 23 or 24
 28 25 or 26
 29 22 and 27 and 28

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	35	21/02/07
<i>Premedline</i>	0	21/02/07
<i>Embase</i>	96	23/02/07
<i>Cochrane Library (except NHSEED)</i>	55	21/02/07
<i>NHSEED</i>	19	21/02/07
<i>Cinahl</i>	20	21/02/07
<i>BNI, Psychinfo, Amed</i>	0 in each	21/02/07
<i>EconLit</i>	2	21/02/07
<i>Web of Science (SCI & SSCI)</i>	83	27/02/07
<i>SIGLE</i>	0	21/02/07

Total References retrieved (after de-duplication): 244

3. Any further comments

This search constituted an update of an HTA report, details as below: ***A rapid and systematic review of the effectiveness and cost-effectiveness of the Taxanes used in the treatment of advanced breast & ovarian cancer (Lister-Sharp et al) September 2000.*** This review last searched for evidence in October 2000, so this search was undertaken from 2000 onwards. The search strategy was taken from the review and criteria for executing it followed accordingly. An additional supplementary search (part b) focusing on the combination of Docetaxel and Gemcitabine only was undertaken with an RCT filter only. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only. The two part search was executed as one search.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	327	20	25/03/08
<i>Premedline (June 27, 2008)</i>	43	3 (already selected)	30/06/08
<i>Embase</i>	598	18	26/03/08
<i>Cochrane Library (Issue 1, 2008)</i>	109	12	26/03/08
<i>Cinahl</i>	76	3	25/03/08
<i>BNI</i>	0	0	25/03/08
<i>Psychinfo</i>	2	0	25/03/08
<i>AMED</i>	1	0	25/03/08
<i>Web of Science (SCI & SSCI)</i>	511	50	27/03/08

Total References retrieved (after de-duplication): 77

Plus 4 additional references picked up from search alerts until 1st July 2008. Final Total: 81

Topic 15 & 16: The appropriate chemotherapy regimes for patients with metastatic breast cancer who are HER2+, following relapse after prior anthracyclines (adjuvant or for metastatic disease) or when anthracycline is inappropriate

The management of patients with metastatic HER2+ breast cancer who a. have had no previous treatment with a biological response modifier, b. have had previous treatment with a biological response modifier, c. are having ongoing treatment with a biological response modifier

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	554	86	14/07/06
<i>Premedline</i>	May 22, 2006 -	76	10	14/07/06
<i>Embase</i>	1980 -	896	95	17/07/06
<i>Cochrane Library</i>	Issue 2, 2006	76	39	14/07/06
<i>Cinahl</i>	1982 -	41	11	14/07/06
<i>BNI</i>	1985 -	9	1	14/07/06
<i>Psychinfo</i>	1806 -	3	0	14/07/06
<i>AMED</i>	1985 -	1	0	14/07/06
<i>SIGLE</i>	1980 - 2005	2	0	14/07/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	983	135	17/07/06
<i>Biomed Central</i>	1997 -	26	1	14/07/06

Total References retrieved (after de-duplication): 255

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	86	15	15/08/06
<i>Premedline</i>	May 22, 2006 -	7	0	15/08/06
<i>Embase</i>	1980 -	328	17	15/08/06
<i>Cochrane Library</i>	Issue 3, 2006	54 (drug only)	17	15/08/06
<i>Cinahl</i>	1982 -	7	5	15/08/06
<i>BNI</i>	1985 -	0	0	15/08/06
<i>Psychinfo</i>	1806 -	0	0	15/08/06
<i>AMED</i>	1985 -	0	0	15/08/06
<i>SIGLE</i>	1980 - 2005	0	0	15/08/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	199	37	15/08/06
<i>Biomed Central</i>	1997 -	56	0	15/08/06

Total References retrieved (after de-duplication): 98

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2000 onwards	475	49	16/08/06
<i>Premedline</i>	2000 onwards	17	1	16/08/06
<i>Embase</i>	2000 onwards	919	51	16/08/06
<i>Cochrane Library</i>	2000 onwards	63	29	16/08/06
<i>Cinahl</i>	2000 onwards	39	6	16/08/06
<i>BNI</i>	2000 onwards	8	0	16/08/06
<i>Psychinfo</i>	2000 onwards	0	0	16/08/06
<i>Amed</i>	2000 onwards	1	0	16/08/06

SIGLE	2000 - 2005	2	0	16/08/06
Web of Science (SCI & SSCI)	2000 onwards	792	57	16/08/06
Biomed Central	2000 onwards	59	1	16/08/06

Total References retrieved (after de-duplication): 115

Medline search strategy (*This search strategy is adapted to each database*)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
- Stage One**
- 21 (herceptin\$ or haerceptin\$.ti,ab,nm
- 22 (trastuzumab or trastuzamab).ti,ab,nm
- 23 21 or 22
- 24 ((HER-2 or HER2) adj3 (neu or positiv\$ or +ive or overexpress\$ or over-express\$ or over express\$ or amplified or amplification)).mp
- 25 ((bB2 or erb-B2 or erbB-2) adj3 (neu or positiv\$ or +ive or overexpress\$ or over-express\$ or over express\$ or amplified or amplification)).mp
- 26 ((c-erbB2 or c-erb-B2 or c-erbB-2) adj3 (neu or positiv\$ or +ive or overexpress\$ or over-express\$ or over express\$ or amplified or amplification)).mp
- 27 (neu adj3 (positiv\$ or +ive or overexpress\$ or over-express\$ or over express\$ or amplified or amplification)).mp.
- 28 (human epidermal growth factor adj3 (neu or positiv\$ or +ive or overexpress\$ or over-express\$ or over express\$ or amplified or amplification)).mp
- 29 (epidermal growth factor adj3 (neu or positiv\$ or +ive or overexpress\$ or over-express\$ or over express\$ or amplified or amplification)).mp
- 30 or/24-29
- 31 23 or 30
- 32 exp Anthracyclines/
- 33 anthracyclin\$.mp.
- 34 32 or 33
- 35 20 and 31 and 34
- 36 20 and 23 and 30
- 37 35 or 36

Stage Two

21 lapatin\$.mp
 22 tykerb.mp
 23 GW572016.mp
 24 avastin\$.mp
 25 bevacizumab\$.mp
 26 or/21-25
 27 20 and 26
 28 (antiVEGF or anti-VEGF).mp
 29 ((rhuMAb adj2 VEGF) or rhuMAbVEGF).mp
 30 ((advance\$ or metastatic) adj cancer\$.mp
 31 29 and 30
 32 20 and 28
 33 31 or 32
 34 27 or 33

Stage Three

35 (herceptin or haerceptin).ti,ab,nm
 36 trastuzumab.ti,ab,nm
 37 1 or 2
 38 exp Breast Neoplasms/all subheadings
 39 (breast\$ adj4 (cancer\$ or tum?r or malignant\$)).ti,ab
 40 (breast\$ adj4 (oncolog\$ or carcinoma\$)).ti,ab
 41 or/4-6
 42 3 and 7
 43 Animals/
 44 Humans/
 45 9 not (9 and 10)
 46 8 not 11

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	17	17/07/06
<i>Premedline</i>	1	17/07/06
<i>Embase</i>	49	17/07/06
<i>Cochrane Library (except NHSEED)</i>	10	17/07/06
<i>NHSEED</i>	3	17/07/06
<i>Cinahl</i>	3	17/07/06
<i>BNI, Psycinfo, AMED</i>	0 in each	17/07/06
<i>EconLit</i>	0	17/07/06
<i>Web of Science (SCI & SSCI)</i>	18	17/07/06
<i>SIGLE</i>	0	17/07/06

Total References retrieved (after de-duplication): 79

3. Any further comments

Just a general exclusions filter applied to basic search for the clinical review as very little data available. Stage Three of the search strategy constituted an update of an HTA report, details as below: ***Systematic review of the clinical effectiveness and cost-effectiveness of herceptin (trastuzumab) for breast cancer (Lewis et al) June 2002.***

This review last searched for evidence in August 2000, so this search was undertaken from 2000 onwards. The search strategy was taken from the review and criteria for executing it followed accordingly. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2006-2008 and English language only. Combined search with Topics 15 and 16, results below cover all.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	425	34	01/05/08
<i>Premedline (June 27, 2008)</i>	42	2 (already selected) + 1	30/06/08
<i>Embase</i>	527	25	01/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	83	21	06/05/08
<i>Cinahl</i>	62	13	06/05/08
<i>BNI</i>	7	0	01/05/08
<i>Psychinfo</i>	2	0	01/05/08
<i>AMED</i>	1	0	01/05/08
<i>Web of Science (SCI & SSCI)</i>	739	97	15/05/08

Total References retrieved (after de-duplication): 132

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 132

NATIONAL COLLABORATING CENTRE FOR CANCER

Advanced Breast Cancer Clinical Guideline

Chapter 5 - Community and Supportive Care

Literature search summary

Topic 3: The ongoing management of cancer patients in the community setting

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	866	39	02/05/07
<i>Premedline</i>	Present file	103	3	04/05/07
<i>Embase</i>	1980 -	1396	14	03/05/07
<i>Cochrane Library</i>	Issue 2, 2007	2500	10	03/05/07
<i>Cinahl</i>	1982 -	33	1	03/05/07
<i>BNI</i>	1994 -	27	2	03/05/07
<i>Psychinfo</i>	1806 -	15	0	04/05/07
<i>SIGLE</i>	1980 - 2005	0	0	04/05/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	147	15	04/05/07
<i>Biomed Central</i>	1997 -	956	0	04/05/07

Total References retrieved (after de-duplication): 52

Medline search strategy (This search strategy is adapted to each database)

1. exp Neoplasms/nu, dt, th
2. antineoplas\$.tw.
3. malignant\$.tw.
4. (leucaemia\$ or leukaemia\$ or leukemia\$).tw.
5. Lymphom\$.tw.
6. (intraepithelial\$ or carcin\$ or tumo?r\$ or cancer\$ or sarcoma\$ or neoplas\$ or oncolog\$ or adeno\$).tw.
7. or/1-6
8. exp Chemotherapy, Adjuvant/

9. exp Neoadjuvant Therapy/
10. exp antineoplastic agents/
11. chemotherap\$.tw.
12. polychemotherap\$.tw.
13. adjuvant therap\$.tw.
14. adjuvant treatment\$.tw.
15. neoadjuvant therap\$.tw.
16. neoadjuvant treatment\$.tw.
17. anticancer therap\$.tw.
18. anti cancer therap\$.tw.
19. anticancer treatment\$.tw.
20. anti cancer treatment\$.tw.
21. antineoplastic therap\$.tw.
22. antineoplastic treatment\$.tw.
23. anti neoplastic therap\$.tw.
24. anti neoplastic treatment\$.tw.
25. antimetabolite\$.tw.
26. or/8-25
27. 7 and 26
28. community.tw.
29. exp community health services/og, st, ut
30. Community medicine/
31. Hospitals, Community/og, st, ut
32. Community Health Centers/og, st, ut
33. exp Outpatient Clinics, Hospital/og, st, ut
34. Outpatients/
35. (outpatient\$ or out-patient\$).ab,ti.
36. exp Home Care Services/og, st, ut
37. home.ab,ti.
38. domiciliary.tw.
39. exp Home Nursing/
40. home nursing.tw.
41. Community Health Nursing/
42. ambulatory care/og, st, ut
43. ambulatory.tw.
44. Day care/og, st, ut
45. day care.tw.
46. outreach.ab,ti.
47. (visiting adj3 (service\$ or clinic\$1 or consultation\$)).tw.
48. primary health care/og, st, ut
49. family practice/og, st, ut
50. general practi\$.tw.
51. port-a-cath\$.tw.
52. intravenous\$ therap\$.tw.
53. exp Home Infusion Therapy/
54. home\$ chemotherap\$.tw.
55. or/28-54
56. managed care/
57. exp inpatients/
58. (inpatient\$ or in-patient\$ or in-hospital\$).ab,ti.
59. cancer care unit\$.tw.
60. exp Cancer Care Facilities/og, st, ut [Organization & Administration, Standards, Utilization]
61. exp Hospital Units/og, st, ut [Organization & Administration, Standards, Utilization]
62. exp Hospitalization/st, og, ut [Standards, Organization & Administration, Utilization]
63. exp Oncology Service, Hospital/og, st, ut [Organization & Administration, Standards, Utilization]

64. exp Hospitals, Special/og, st, ut [Organization & Administration, Standards, Utilization]
 65. or/56-64
 66. 27 and 55
 67. 27 and 65
 68. 66 and 67

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	164	10/05/07
<i>Premedline</i>	6	10/05/07
<i>Embase</i>	332	10/05/07
<i>Cochrane Library (except NHSEED)</i>	366	10/05/07
<i>NHSEED</i>	298	10/05/07
<i>Cinahl</i>	51	10/05/07
<i>BNI</i>	3	10/05/07
<i>Pyschinfo</i>	16	10/05/07
<i>EconLit</i>	0	10/05/07
<i>Web of Science (SCI & SSCI)</i>	42	10/05/07
<i>SIGLE</i>	0	10/05/07

Total References retrieved (after de-duplication): 1050

3. Any further comments

RCT filter applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2007-2008 and English language only.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 5/2008	26	3	19/05/08
<i>Premedline</i>	2007 – 5/2008	144	16	19/05/08
<i>Embase</i>	2007 – 5/2008	331	1	19/05/08
<i>Cochrane Library</i>	2007 – 5/2008	310	1	19/05/08
<i>Cinahl</i>	2007 – 5/2008	9	2	19/05/08
<i>BNI</i>	2007 – 5/2008	4	2	19/05/08
<i>Psychinfo</i>	2007 – 5/2008	4	0	19/05/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 5/2008	14	0	19/05/08
<i>Biomed Central</i>	2007 – 5/2008	155	0	19/05/08

Total References retrieved (after de-duplication): 24

Topic 26: What are the effective interventions used to support young families in which a parent has advanced breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966 -	1444	376	14/11/06
Premedline	Present file	84	39	15/11/06
Embase	1980 -	640	106	01/12/06
Cochrane Library	Issue 4, 2006	595	83	04/12/06
Cinahl	1982 -	307	103	18/12/06
BNI	1994 -	44	32	18/12/06
Psychinfo	1967 -	488	210	18/12/06
SIGLE	1980 - 2005	0	0	22/01/07
Web of Science (SCI & SSCI)	1970 -	290	51	26/01/07
Biomed Central	1997 -	65	0	24/12/06

Total References retrieved (after de-duplication): 794

Medline search strategy (*This search strategy is adapted to each database*)

1. exp breast neoplasms/
2. exp " Neoplasms, Ductal, Lobular, and Medullary"/
3. exp breast/
4. exp neoplasms/
5. 3 and 4
6. (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or dcis or ductal or infiltrat\$ or intraductal\$ or lobular or medullary)).mp.
7. exp mammary neoplasms/
8. (mammary\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or dcis or ductal or infiltrat\$ or intraductal\$ or lobular or medullary)).mp.
9. or/1-2,5-8
10. exp infant/
11. exp child/
12. exp adolescent/
13. exp minors/
14. (neonat\$ or perinat\$ or baby or babies or toddler\$ or kid\$ or child\$ or schoolage\$ or juvenile\$ or adolescen\$ or youth\$ or teen\$ or minor\$ or boy\$ or girl\$).mp.
15. exp family/
16. exp "child of impaired parents"/
17. (famil\$ or parent\$ or mother\$ or father\$ or son\$ or daughter\$).mp.
18. or/10-17
19. exp education/
20. exp psychotherapy/
21. exp cognitive therapy/
22. exp counseling/
23. exp self help groups/
24. exp social support/
25. exp hotlines/
26. exp telephone/
27. exp Internet/
28. ((hot or help\$ or tele\$) adj line\$).mp.
29. (internet or website\$).mp.
30. (advis\$ or educat\$ or counsel\$ or intervent\$).mp.
31. ((cognit\$ or group\$ or psycho\$) adj (therap\$ or supp\$ or session\$)).mp.
32. ((self help\$ or supp\$ or counsel\$) adj (group\$ or session\$)).mp.
33. or/19-32

34. 9 and 18 and 33

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	121	04/01/07
<i>Premedline</i>	5	22/01/07
<i>Embase</i>	447	04/01/07
<i>Cochrane Library (except NHSEED)</i>	100	04/01/07
<i>NHSEED</i>	17	04/01/07
<i>Cinahl</i>	160	04/01/07
<i>BNI</i>	0	22/01/07
<i>Psychinfo</i>	32	22/01/07
<i>EconLit</i>	0	22/01/07
<i>Web of Science (SCI & SSCI)</i>	49	26/01/07
<i>SIGLE</i>	0	22/01/07

Total References retrieved (after de-duplication): 779

3. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2006-2008 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	323	1	12/05/08
<i>Premedline (June 27, 2008)</i>	37	0	30/06/08
<i>Embase</i>	239	0	14/05/08
<i>Cochrane Library</i>	451	0	13/05/08
<i>Cinahl</i>	42	0	12/05/08
<i>BNI</i>	18	0	12/05/08
<i>Psychinfo</i>	121	2	12/05/08
<i>AMED</i>	6	1	12/05/08
<i>Web of Science (SCI & SSCI)</i>	127	1	12/05/08

Total References retrieved (after de-duplication): 5

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 5

NATIONAL COLLABORATING CENTRE FOR CANCER

Advanced Breast Cancer Clinical Guideline

Chapter 6 - Management of Specific Problems

Literature search summary

Topic 21: The management of lymphoedema in breast cancer patients, a. who have completed their primary treatment and have no active disease, b. have local regional recurrent disease

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966 -	424 (with filters)	113	19/06/07
Premedline	June 18, 2007	33	6	19/06/07
Embase	1980 -	595 (with filters)	86	20/06/07
Cochrane Library	Issue 2, 2007	183	70	19/06/07
Cinahl	1982 -	68 (with filters)	23	19/06/07
BNI	1994 -	37	14	19/06/07
Psychinfo	1806 -	21	5	19/06/07
AMED	1985 -	60	18	19/06/07
SIGLE	1980 - 2005	10	0	19/06/07
Web of Science (SCI & SSCI)	1970 -	765	129	20/06/07
Biomed Central	1997 -	46	1	19/06/07

Total References retrieved (after de-duplication): 246

Medline search strategy (*This search strategy is adapted to each database*)

1 exp Breast Neoplasms/
 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
 3 Carcinoma, Intraductal, Noninfiltrating/
 4 Carcinoma, Lobular/
 5 Carcinoma, Medullary/
 6 exp mammary neoplasms/
 7 or/1-6
 8 exp Breast/
 9 breast.tw.
 10 8 or 9
 11 (breast adj milk).tw.
 12 (breast adj tender\$.tw.
 13 11 or 12
 14 10 not 13
 15 exp Neoplasms/
 16 14 and 15
 17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 19 Paget's Disease, Mammary/
 20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 21 or/17-20
 22 7 or 21
 23 exp Mastectomy/

24 (mastectom\$ or post?mastectom\$ or post-mastectom\$).mp.
 25 (segmentectom\$ or post?segmentectom\$).mp.
 26 (lumpectom\$ or post?lumpectom\$).mp.
 27 (quadrectom\$ or post?quadrectom\$).mp.
 28 ((breast\$ or mammary) adj4 surg\$).mp.
 29 (breast\$ adj4 (radiation or radiotherap\$)).mp.
 30 or/23-29
 31 22 or 30
 32 exp Lymphedema/
 33 lymph?ed\$.mp.
 34 elephantiasis.mp.
 35 (arm\$ adj4 (morbidity or swell\$ or swollen or pain\$ or oedema or edema)).mp.
 36 (upper limb\$ adj4 (morbidity or swell\$ or swollen or pain\$ or oedema or edema)).mp.
 37 (lymph\$ adj4 (oedema or edema)).mp.
 38 Edema/
 39 (upper limb\$ or arm\$).mp.
 40 38 and 39
 41 or/32-37
 42 40 or 41
 43 31 and 42

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	18	07/06/06
<i>Premedline</i>	3	07/06/06
<i>Embase</i>	53	07/06/06
<i>Cochrane Library (except NHSEED)</i>	30	07/06/06
<i>NHSEED</i>	3	07/06/06
<i>Cinahl</i>	37	07/06/06
<i>BNI</i>	0	07/06/06
<i>Psychinfo</i>	4	07/06/06
<i>AMED</i>	11	07/06/06
<i>EconLit</i>	0	07/06/06
<i>Web of Science (SCI & SSCI)</i>	41	07/06/06
<i>SIGLE</i>	0	07/06/06

Total References retrieved (after de-duplication): 159

3. Any further comments

Systematic reviews (2002+), RCT and Observational filters applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only. Search was executed for both Early and Advanced BC guidelines together.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	56	23	10/04/08
<i>Premedline (June 27, 2008)</i>	3	1	30/06/08
<i>Embase</i>	115	17	10/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	38	14	24/04/08

Cinahl	20	6	10/04/08
BNI	0	0	10/04/08
Psychinfo	10	0	10/04/08
AMED	3	0	10/04/08
Web of Science (SCI & SSCI)	218	35	10/04/08

Total References retrieved (after de-duplication): 50

1 additional reference picked up from search alerts until 1st July 2008. Final Total: 51

Topic 25: The role of cancer-related fatigue management in advanced breast cancer

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966 -	808	101	15/05/07
Premedline	May 14, 2007	31	5	15/05/07
Embase	1980 -	1638	146	16/05/07
Cochrane Library	Issue 2, 2007	198	45	16/05/07
Cinahl	1982 -	278	94	15/05/07
BNI	1994 -	43	18	15/05/07
Psychinfo	1806 -	120	37	15/05/07
Amed	1985 -	44	21	15/05/07
SIGLE	1980 - 2005	1	1	15/05/07
Web of Science (SCI & SSCI)	1970 -	1523	213	17/05/07
Biomed Central	1997 -	74	0	15/05/07

Total References retrieved (after de-duplication): 345

Medline search strategy (*This search strategy is adapted to each database*)

1 exp Breast Neoplasms/
2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
3 Carcinoma, Intraductal, Noninfiltrating/
4 Carcinoma, Lobular/
5 Carcinoma, Medullary/
6 exp mammary neoplasms/
7 or/1-6
8 exp Breast/
9 breast.tw.
10 8 or 9
11 (breast adj milk).tw.
12 (breast adj tender\$.tw.
13 11 or 12
14 10 not 13
15 exp Neoplasms/
16 14 and 15
17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
19 Paget's Disease, Mammary/
20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
21 or/17-20

22 7 or 21
 23 exp Fatigue/
 24 fatigu\$.ti,ab.
 25 (exhaust\$ or tired\$ or weary or weariness).ti,ab.
 26 (low adj energy).ti,ab.
 27 or/23-26
 28 22 and 27

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	48	17/05/07
<i>Premedline</i>	4	17/05/07
<i>Embase</i>	99	17/05/07
<i>Cochrane Library (except NHSEED)</i>	34	17/05/07
<i>NHSEED</i>	2	17/05/07
<i>Cinahl</i>	139	17/05/07
<i>BNI</i>	1	17/05/07
<i>Psychinfo</i>	7	17/05/07
<i>AMED</i>	7	17/05/07
<i>EconLit</i>	0	17/05/07
<i>Web of Science (SCI & SSCI)</i>	148	17/05/07
<i>SIGLE</i>	0	17/05/07

Total References retrieved (after de-duplication): 361

3. Any further comments

Just a general exclusions filter applied to basic search for the clinical review as very little data available. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Supplementary Literature search details

(a) Non-pharmacological Interventions for Advanced Cancer Patients

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2003 - , 2005 -	1032	71	03/12/07
<i>Premedline</i>	Nov 28, 2007	198	4	29/11/07
<i>Embase</i>	2003 - , 2005 -	719	54	04/12/07
<i>Cochrane Library</i>	Issue 4, 2007	1124	76	03/12/07
<i>Cinahl</i>	1982 -	165	33	29/11/07
<i>BNI</i>	1994 -	6	0	29/11/07
<i>Psychinfo</i>	1806 -	25	4	29/11/07
<i>Amed</i>	1985 -	34	8	29/11/07
<i>Web of Science (SCI & SSCI)</i>	2005 -	437	54	04/12/07

A general exclusions filter was used in all databases. Main focus was to identify RCTs so basic Cochrane Library search was supplemented by searches in Medline and Embase (RCT filter: 2005 onwards and Systematic Review filter: 2003 onwards), and then all databases were searched without date limit and an RCT filter when appropriate.

1 exp Neoplasms/
 2 cancer\$.mp.
 3 1 or 2
 4 exp Fatigue/
 5 (exhaust\$ or tired\$ or weary or weariness).ti,ab.
 6 (low adj energy).ti,ab.

7 fatigu\$.ti,ab.
8 or/4-7
9 3 and 8

(b) Corticosteroids for Advanced Breast Cancer Patients

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	261	24	20/11/07
<i>Premedline</i>	Nov 14, 2007	6	1	20/11/07
<i>Embase</i>	1980 -	321	14	20/11/07
<i>Cochrane Library</i>	Issue 4, 2007	88	13	20/11/07
<i>Cinahl</i>	1982 -	30	6	20/11/07
<i>BNI</i>	1994 -	2	1	20/11/07
<i>Psychinfo</i>	1806 -	19	1	20/11/07
<i>Amed</i>	1985 -	13	3	20/11/07
<i>SIGLE</i>	1980 - 2005	0	0	20/11/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	210	32	20/11/07
<i>Biomed Central</i>	1997 -	32	0	20/11/07

Just a general exclusions filter applied to basic search for the clinical review as very little data available.

1 exp Neoplasms/
2 cancer\$.mp.
3 fatigu\$.mp.
4 1 or 2
5 3 and 4
6 exp Adrenal Cortex Hormones/
7 exp Megestrol Acetate/
8 51154-23-5.rn.
9 (megestrol adj acetat\$).mp.
10 megace.mp.
11 exp Prednisolone/
12 50-24-8.rn.
13 (methylprednisolon\$ or prednisolon\$).mp.
14 exp Prednisone/
15 53-03-2.rn.
16 (prednison\$ or sterapred\$).mp.
17 exp Dexamethasone/
18 50-02-2.rn.
19 (dexamethason\$ or decadron\$).mp.
20 corticosteroid\$.mp.
21 or/6-20
22 5 and 21
23 (terminal\$ adj (cancer\$ or ill\$ or care)).ti,ab.
24 (palliativ\$ adj (cancer\$ or ill\$ or care)).ti,ab.
25 23 or 24
26 4 and 21 and 25
27 22 or 26

5. Update Search

(a) Non-pharmacological Interventions for Advanced Cancer Patients

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2007-2008 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search

<i>Medline</i>	53	5	14/05/08
<i>Premedline (June 27, 2008)</i>	32	2 (already selected)	30/06/08
<i>Embase</i>	119	6	14/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	49	7	14/05/08
<i>Cinahl</i>	28	8	15/05/08
<i>BNI</i>	1	0	14/05/08
<i>Psychinfo</i>	3	1	14/05/08
<i>AMED</i>	2	1	14/05/08
<i>Web of Science (SCI & SSCI)</i>	223	14	15/05/08

(b) Corticosteroids for Advanced Cancer Patients

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2007-2008 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	25	5	15/05/08
<i>Premedline (June 27, 2008)</i>	0	0	30/06/08
<i>Embase</i>	60	3	15/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	5	4	15/05/08
<i>Cinahl</i>	5	2	15/05/08
<i>BNI</i>	0	0	15/05/08
<i>Psychinfo</i>	2	1	15/05/08
<i>AMED</i>	3	0	15/05/08
<i>Web of Science (SCI & SSCI)</i>	33	4	15/05/08

Total References retrieved (after de-duplication) for parts a & b together: 35
Plus 1 additional reference. Final Total: 36

(c) CRF Treatment in Advanced Breast Cancer Patients

For the update search, the search was executed as originally, date limit 2007-2008 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	129	19	16/05/08
<i>Premedline (June 27, 2008)</i>	10	1 (already selected)	30/06/08
<i>Embase</i>	304	17	16/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	30	9	16/05/08
<i>Cinahl</i>	58	6	16/05/08
<i>BNI</i>	15	2	16/05/08
<i>Psychinfo</i>	38	6	16/05/08
<i>AMED</i>	13	0	16/05/08
<i>Web of Science (SCI & SSCI)</i>	325	32	16/05/08

Total References retrieved (after de-duplication): 45

Topic 22: The management of patients with uncontrolled local disease in the presence of metastases or following primary treatment

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	806	89	05/02/07
<i>Premedline</i>	Feb 5, 2007	52	0	05/02/07

Embase	1980 -	1443	75	07/02/07
Cochrane Library	Issue 1, 2007	87	6	06/02/07
Cinahl	1982 -	77	66	06/02/07
BNI	1994 -	59	47	05/02/07
Psychinfo	1806 -	6	1	05/02/07
AMED	1985 -	14	7	05/02/07
SIGLE	1980 - 2005	3	2	05/02/07
Web of Science (SCI & SSCI)	1970 -	1148	47	06/02/07
Biomed Central	1997 -	10	0	05/02/07

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966 -	526	88	14/02/07
Premedline	Present file	27	5	14/02/07
Embase	1980 -	337	43	16/02/07
Cochrane Library	Issue 1, 2007	23	1	15/02/07
Cinahl	1982 -	32	5	14/02/07
BNI	1994 -	1	0	14/02/07
Psychinfo	1806 -	3	0	14/02/07
AMED	1985 -	4	1	14/02/07
SIGLE	1980 - 2005	0	0	15/02/07
Web of Science (SCI & SSCI)	1970 -	361	94	15/02/07
Biomed Central	1997 -	27	2	15/02/07

Total References retrieved (after de-duplication): 359

Medline search strategy (*This search strategy is adapted to each database*)

1 exp Breast Neoplasms/
2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
3 Carcinoma, Intraductal, Noninfiltrating/
4 Carcinoma, Lobular/
5 Carcinoma, Medullary/
6 exp mammary neoplasms/
7 or/1-6
8 exp Breast/
9 breast.tw.
10 8 or 9
11 (breast adj milk).tw.
12 (breast adj tender\$.tw.
13 11 or 12
14 10 not 13
15 exp Neoplasms/
16 14 and 15
17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
19 Paget's Disease, Mammary/
20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
21 or/17-20
22 7 or 21
23 exp Neoplasm Metastasis/
24 ((breast\$ or mammar\$) adj5 (metastat\$ or advance\$ or second\$ or recurren\$ or inoperab\$ or disseminat\$ or incur\$)).mp.

25 (breast\$ or mammar\$).mp.
26 ((stage or grade or type) adj3 ("3" or "4" or c or d or iii\$ or iv\$)).mp.
27 (N1 or N2\$ or N3\$ or pN1\$ or pN2\$ or pN3\$).mp.
28 26 or 27
29 25 and 28
30 23 or 24 or 29
31 22 and 30
32 Necrosis/
33 exp Skin Care/
34 Skin Neoplasms/sc [Secondary]
35 ((skin or cutaneous) adj4 (metast\$ or involv\$ or tumour\$ or tumor\$ or lesion\$ or wound\$ or carcinoma\$)).mp.
36 (fungat\$ adj10 (lesion\$ or wound\$ or tumor\$ or tumour\$ or cancer\$ or breast cancer\$ or carcinoma\$ or mass or neoplasm\$)).mp.
37 (ulcer\$ adj2 (carcinoma\$ or lesion\$ or wound\$ or tumor\$ or tumour\$ or cancer\$ or breast cancer\$ or mass or neoplasm\$)).mp.
38 cancer\$ wound\$.mp.
39 uncontrol\$ local disease\$.mp.
40 (mucinous\$ adj2 (breast cancer\$ or breast carcinoma\$ or breast tumour\$ or breast tumor\$)).mp.
41 or/32-40
42 31 and 41
43 Adenocarcinoma, Mucinous/
44 exp Breast Neoplasms/ or exp Breast/
45 43 and 44
46 30 and 45
47 42 or 46
48 *Phosphorylcholine/
49 miltefosine.ti,ab.
50 *Metronidazole/
51 metronidazole.ti,ab.
52 *Debridement/
53 maggot\$.ti,ab.
54 (larva\$ adj (therap\$ or treatment\$)).ti,ab.
55 or/48-54
56 31 and 55
57 47 or 56
58 36 or 57
Extra search done (results in second results box above)
59 ((locally advanced or locally recurrent) adj (breast cancer or breast carcinoma)).mp.
60 ((chest wall or thoracic wall) adj3 (reconstruct\$ or resect\$)).mp.
61 (palliative adj2 resect\$).mp.
62 [60 or 61 (and then put with general breast cancer search)] or 59

2. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. Health economics search not required.

3. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2006-2008 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	214	9	09/05/08
<i>Premedline (June 27, 2008)</i>	10	0	30/06/08
<i>Embase</i>	313	4	09/05/08
<i>Cochrane Library</i>	117	1	09/05/08
<i>Cinahl</i>	21	2	12/05/08
<i>BNI</i>	13	9	09/05/08
<i>Psychinfo</i>	0	0	09/05/08
<i>AMED</i>	4	2	09/05/08
<i>Web of Science (SCI & SSCI)</i>	308	2	12/05/08

Total References retrieved (after de-duplication): 18

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 18

Topic 18: The management of metastatic bone disease (inc. bisphosphonates, samarium, radiotherapy, surgery and rehabilitation)

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1477	553	19/09/06
<i>Premedline</i>	Present file	66	18	20/09/06
<i>Embase</i>	1980 -	1293	381	21/09/06
<i>Cochrane Library</i>	Issue 3, 2006	259	64	03/10/06
<i>Cinahl</i>	1982 -	115	25	03/10/06
<i>BNI</i>	1994 -	73	6	03/10/06
<i>Psychinfo</i>	1806 -	68	2	03/10/06
<i>SIGLE</i>	1980 - 2005	9	5	03/10/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	142	74	09/10/06
<i>Biomed Central</i>	1997 -	131	14	10/10/06

Total References retrieved (after de-duplication): 917

Medline search strategy (This search strategy is adapted to each database)

1 exp Breast Neoplasms/

2 exp "Neoplasms, Ductal, Lobular, and Medullary"/

3 exp breast/

4 exp neoplasms/

5 3 and 4

6 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or dcis or ductal or infiltrat\$ or intraductal\$ or lobular or medullary)).mp.

7 exp mammary neoplasms/

8 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or dcis or ductal or infiltrat\$ or intraductal\$ or lobular or medullary)).mp.

9 or/1-2,5-8

10 exp bone neoplasms/sc

11 exp neoplasm metastasis/
12 exp "bone and bones"/
13 11 and 12
14 ((bone\$ or skelet\$ or osseous or osteo\$) adj5 (second\$ or metast\$ or spread\$ or advanc\$ or termina\$)).mp.
15 10 or 13 or 14
16 exp hypercalcemia/
17 exp Fractures, Bone/
18 exp spinal cord compression/
19 (hypercalc\$ or fractur\$ or break\$ or compress\$).mp.
20 or/16-19
21 exp neoplasms/
22 20 and 21
23 15 or 22
24 9 and 23
25 exp radiotherapy/
26 ((radiotherap\$ or radiat\$) adj (therapy or treat\$)).tw.
27 exp Diphosphonates/
28 (bisphosphonat\$ or disphosphonat\$).mp.
29 (etidron\$ or didron\$ or difosfen\$ or osteodidronel or osteum).mp.
30 "disodium dihydrogen(1-hydroxyethylidene)diphosphonate".mp.
31 (pamidronate or APD or aredia).mp.
32 "disodium 3-amino-1-hydroxypropylidenebisphosphonate".tw.
33 (clodronate or bonefos or loron or ascredar or lodronat\$ or lytos or ostac or clastoban or clasteon or difosonal).tw.
34 (ossiten or mebonat\$ or tiludron\$ or skelid or risedron\$ or actonel).tw.
35 (alendron\$ or fosemax or adronat\$ or alendros or dronal or neridron\$ or AHDP).tw.
36 (zoledron\$ or zometa or ibandron\$ or bondronat\$ or incadron or olpadron\$ or OPD or YM175 or YM529 or minodron\$).tw.
37 exp drug therapy/
38 exp Antineoplastic Agents/
39 ((chemotherapy or antineoplastic or anticancer) adj3 (agent\$ or protocol\$ or regimen\$)).tw.
40 exp Antineoplastic Combined Chemotherapy Protocols/
41 (endocrin\$ adj3 (treatment\$ or therap\$)).mp.
42 exp Surgery/
43 exp Surgical Procedures, Operative/
44 exp Rehabilitation/
45 exp Exercise Therapy/
46 Acupuncture Therapy/ or Acupuncture Analgesia/ or Acupuncture/
47 exp Relaxation/
48 exp Massage/
49 exp Analgesia/
50 or/25-49
51 24 and 50

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	95	20/10/06
<i>Premedline</i>	2	20/10/06
<i>Embase</i>	90	20/10/06
<i>Cochrane Library (except NHSEED)</i>	-	20/10/06
<i>NHSEED</i>	25	20/10/06
<i>Cinahl</i>	12	20/10/06
<i>BNI</i>	8	20/10/06
<i>Psychinfo</i>	6	20/10/06
<i>EconLit</i>	27	20/10/06
<i>Web of Science (SCI & SSCI)</i>	68	20/10/06
<i>SIGLE</i>	0	20/10/06

Total References retrieved (after de-duplication): 242

3. Any further comments

Systematic reviews (2002+), RCT and Observational filters applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	292	39	29/04/08
<i>Premedline (June 27, 2008)</i>	11	4 (already selected)	30/06/08
<i>Embase</i>	530	30	30/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	79	9	29/04/08
<i>Cinahl</i>	73	8	30/04/08
<i>BNI</i>	4	0	30/04/08
<i>Psychinfo</i>	5	1	30/04/08
<i>AMED</i>	9	3	30/04/08
<i>Web of Science (SCI & SSCI)</i>	468	72	30/04/08

Total References retrieved (after de-duplication): 90

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 90

Topic 19: The management of metastatic brain and meningeal disease (surgery, stereotactic radiotherapy, external beam radiotherapy, intrathecal chemotherapy, rehabilitation)

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	618	168	16/02/07
<i>Premedline</i>	Feb 15, 2007	13	7	19/02/07
<i>Embase</i>	1980 -	1494	128	20/02/07
<i>Cochrane Library</i>	Issue 1, 2007	79	25	19/02/07

Cinahl	1982 -	19	2	19/02/07
BNI	1994 -	0	0	19/02/07
Psychinfo	1806 -	9	0	19/02/07
AMED	1985 -	8	0	19/02/07
SIGLE	1980 - 2005	11	0	19/02/07
Web of Science (SCI & SSCI)	1970 -	1081	150	20/02/07
Biomed Central	1997 -	81	2	20/02/07

Total References retrieved (after de-duplication): 305

Medline search strategy (*This search strategy is adapted to each database*)

1 exp brain neoplasms/ or exp meningeal neoplasms/ or exp Spinal Neoplasms/
2 ((brain or intracranial or cerebral) adj5 metastas#s).mp.
3 metastatic brain.tw.
4 (meninge\$ adj5 (disease\$ or carcinoma\$ or tumour\$ or tumor\$ or spread or carcinosis or involvement or metast\$)).ti,ab.
5 ((brain or intracranial or cerebral or meninge\$) adj5 (second\$ or metast\$ or spread\$ or advanc\$ or termina\$)).mp.
6 ((CNS or central nervous system\$) adj5 (disease\$ or carcinoma\$ or tumour\$ or tumor\$ or spread or carcinosis or involvement or metast\$)).ti,ab.
7 or/1-6
8 exp Neoplasm metastasis/
9 exp Brain/
10 exp Meninges/
11 9 or 10
12 8 and 11
13 7 or 12
14 exp Breast Neoplasms/
15 exp "Neoplasms, Ductal, Lobular, and Medullary"/
16 Carcinoma, Intraductal, Noninfiltrating/
17 Carcinoma, Lobular/
18 Carcinoma, Medullary/
19 exp mammary neoplasms/
20 or/14-19
21 exp Breast/
22 breast.tw.
23 21 or 22
24 (breast adj milk).tw.
25 (breast adj tender\$).tw.
26 24 or 25
27 23 not 26
28 exp Neoplasms/
29 27 and 28
30 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
31 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
32 Paget's Disease, Mammary/
33 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
34 or/30-33
35 20 or 34
36 13 and 35

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	13	20/02/07
<i>Premedline</i>	0	20/02/07
<i>Embase</i>	97	20/02/07
<i>Cochrane Library (except NHSEED)</i>	27	20/02/07
<i>NHSEED</i>	6	20/02/07
<i>Cinahl</i>	4	20/02/07
<i>BNI</i>	0	20/02/07
<i>Psychinfo</i>	0	20/02/07
<i>AMED</i>	1	20/02/07
<i>EconLit</i>	0	20/02/07
<i>Web of Science (SCI & SSCI)</i>	20	20/02/07
<i>SIGLE</i>	0	20/02/07

Total References retrieved (after de-duplication): 155

3. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2006-2008 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	148	25	07/05/08
<i>Premedline (June 27, 2008)</i>	13	1 (already selected) + 3	30/06/08
<i>Embase</i>	118	24	09/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	24	3	07/05/08
<i>Cinahl</i>	12	1	08/05/08
<i>BNI</i>	0	0	08/05/08
<i>Psychinfo</i>	2	0	08/05/08
<i>AMED</i>	1	0	08/05/08
<i>Web of Science (SCI & SSCI)</i>	351	33	08/05/08

Total References retrieved (after de-duplication): 60

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 60

Appendix B – Position paper. Management of Uncontrolled Local Disease in Patients with Advanced Breast Cancer

A review of this subject was commissioned by the National Collaborating Centre for Cancer in Wales. An expert panel was convened in order to write this position paper. The panel members who drew up the paper were:

Members of the working group:

Mrs Samantha Holloway¹, Lecturer, Department of Wound Healing, School of Medicine, Cardiff University

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Ms Helen McGarrigle², Clinical Nurse Specialist (Breast Care), Cardiff Breast Unit, Llandough Hospital, Penlan Rd, Llandough, Vale of Glamorgan

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Mrs Sue Scarrott², Specialist Nurse (Breast Care), Gloucestershire Hospitals NHS Foundation Trust. Cheltenham. Glos

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Acknowledgements

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<p>¹ Author ² Reviewers</p>

1.0 Executive Summary

In contrast to other types of disease processes the primary outcome for individuals with uncontrolled disease in advanced local breast cancer is to ensure their quality of life (QoL) as cure may no longer be an option. For the purposes of this paper uncontrolled disease is taken to describe Fungating Breast Wounds (FBW), therefore the remainder of this paper will consider this as the focus.

There are a number of secondary outcomes that should also be taken into consideration to ensure the appropriate local wound management and therefore patient comfort. These will include:

- ✦ Management of Malodour
- ✦ Exudate Management
- ✦ Reduce risk of haemorrhage
- ✦ Management of pain
- ✦ Cosmetic appearance
- ✦ Improve Quality of Life
- ✦ Tumour containment

This paper will focus on management strategies in relation to the majority of these, however tumour containment is considered to be outside of the scope of this review.

Randomised Controlled Trials (RCT) are viewed as the gold standard for providing evidence, however this is challenging in patients with FBW due to the nature of the disease (Morison et al 1997, Seaman 2006). Therefore the information regarding the assessment and local wound management of patients with (FBW) is primarily derived from literature in nursing which in turn is based on expert opinion and personal experience (Grocott 1995b, Morison et al 1997, Burns and Stephens 2003, Seaman 2006, Lazelle-Ali 2007). Adderley and Smith (2007) suggest that multiple case study designs, such as those by Grocott and Cowley (2001) maybe the highest level of evidence that can be evaluated.

The view of the majority of authors is that such wounds are a particular challenge (Lavery 2003) and require practitioners to be flexible in their approach to managing the patient (Morison et al 1997, Wilson 2005, Bale and Jones 2006). It is not unusual for patients suffering with FBW to be cared for in the community (Young 1997a, Draper 2005) and often in their own home. This obviously requires that the community nursing team caring for the patient be fully converse with the actual and potential problems the patient may have, and also be able to allay the concerns of the patient and family (Wilson 2005).

2.0 Key Recommendations

- 2.1 That population – based registers include collection of data related to the incidence of fungating wounds, to include FBW
- 2.2 Evidence other than findings from RCTs may need to be considered in terms of developing national guidance. This should include evidence gained from expert opinion, case series and case studies.
- 2.3 Patient assessment and subsequent management should take into account presenting problems from the patient's perspective and existing standards for assessment should be considered to document the progress of interventions and to improve quality of life.
- 2.4 Currently best practice advocates the use of existing dressing products to manage patients with FBW. However dressing manufacturers should consider the unique needs of patients with FBW and examine the need for a wider range of products. This should include new developments for exudate and pain management as well as the treatment of malodour. There are systems in place already to carry this forward, i.e. WRAP (Browne et al 2004).
- 2.5 In the absence of evidence for the management of patients with FBW current practice indicates that practitioners follow the principles of moist wound healing and wound bed preparation, however such beliefs are based on data that is aimed at wound healing. However in the palliative setting it may be that amelioration rather than healing needs to be considered.
- 2.6 Whilst the care of patients with FBW should include a multi-disciplinary approach with MDT clinics where possible, often the physical and psychological problems that a patient faces results in them feeling embarrassed or anxious about having to deal with a number of professionals. Therefore Health Care Professionals should consider the needs of the patient and, where possible and appropriate, limit the number of individuals required to provide direct patient care.

3.0 Mission Statement

- 3.1 People with fungating breast wounds (FBW) require access to health care professionals who have an in-depth understanding of their presenting problems and who have knowledge of the appropriate management options available. Such a service should be able to offer the individual a choice of local treatments and in addition ensure the persons safety, therefore minimising any risks. The management plan must also take into account the individual's physical and psychological well-being and formulate a plan of care that is consistent with the patient's priorities and wishes.

4.0 Philosophy of Care

- 4.1 There is existing guidance that identifies the systems and services that need to be established in order to provide patients with the required level of care (NICE 2002, WHO 2007).

"Every patient with advanced, recurrent or metastatic disease should be treated by a breast cancer multidisciplinary team (MDT) which includes a specialist oncologist. The team should have close links with a pain specialist and orthopaedic services."

NICE (2002, pg65)

In addition to those services identified above it would also be advisable to include individuals who have specialist knowledge or experience of wound management in patients with FBW.

- 4.2 Patients with locally advanced (T4) tumours are likely to have metastatic disease which affects many organs and tissues, therefore these patients need to be managed jointly by the specialist breast cancer MDT and also palliative care teams (NICE 2002).

Palliative Care is defined as:

"...an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment, and treatment of pain and other problems – physical, psychosocial and spiritual."

(WHO 2007, pg3)

Therefore it is these that should guide the overriding structure of the services that are provided and include acknowledgement of the range of problems and specialists involved. Cawley and Webber (1995) had previously suggested that palliative care may be required for a considerable length of time because improved methods of treatment mean that patients are surviving for longer. In addition treatments may be considered at fairly advanced stages of the disease process (Cawley and Webber 1995).

5.0 National Context

- 5.1 There are existing recommendations that outline service models that should be adopted and in addition provide a framework for developing high quality services for patients with cancer and support for their family / carers (NICE 2004)

5.2 Previous initiatives outlined in, *The NHS Plan, The NHS Cancer Plan and Improving Health in Wales* provide recommendations on all aspects of cancer care (NICE 2006). Therefore this position paper should be considered in conjunction with these standards.

6.0 Extent of the Problem

6.1 Grocott (2000a, 2000b) has highlighted that the true incidence of FW (to include FBW) is an unknown quantity as there is no formal reporting mechanism currently in terms of population-based cancer registers. This is supported by other authors (Draper 2005, Adderley and Smith 2007). In addition there is a lack of accurate data to establish the extent of FBW (Ivetic and Lyne 1990). Morison et al (1997) highlight the difficulties of applying findings from older studies as changes in screening; prevention and treatment make comparisons difficult.

6.2 According to the Royal College of Radiologists there are 320 clinical oncologists in the U.K. (RCR 2008). Recent personal communications to try and establish the number of patients with FBW that may present to an oncologist or Breast Care Nurse has identified that there are probably 1-2 patients per month in Cardiff and Vale NHS Trust (Barrett-Lee 2008, McGarrigle 2008). Based on the minimum potential figure of 1 patient presenting every month to each clinical oncologist it could be estimated that there are potentially 3840 patients with FBW seen per year). However what is not so clear is the duration of FBW care in terms of months/weeks. Whilst the overall number of individuals appears small, the impact of having a FBW pervades many aspects of the patient's day-to-day life.

7.0 Definition

7.1 Fungating describes a malignant growth which is usually ulcerative and proliferative (Mortimer 2004). They have been described as 'fungus-like' or have a 'cauliflower-like' appearance (Collier 2000). However they often vary in their appearance (Grocott 1999).

8.0 Aetiology

8.1 Fungating Wounds: Other terms that are used:

- Ulcerating tumours
- Malignant wounds
- Neoplastic lesions
- Cutaneous metastatic Disease (Manning 1998)

8.1.1 FBW may result from a primary cancer or from metastases that spread to the skin from a local or distant tumour (Bryant 2000, Langemo et al 2007, Naylor 2001, Grocott 2007a). Such wounds are most commonly associated with breast cancer (Wilson 2005). The wound often appears as a cauliflower-like structure as the tumour grows (Collier 1997). Commonly the tumour ulcerates to form craters, sinuses or fistulae. The underlying tissue, capillaries and lymph vessels are often involved and subsequently destroyed. This decrease in vascularity and ulceration often leads to further problems (Grocott 2000a, 2000b) such as infection and friable tissue that can bleed easily or even lead to haemorrhage.

8.1.2 FBW commonly occur near the end of life (Langemo et al 2007) often in the last 6 months of life (Naylor 2001) and rarely heal. Management is aimed at palliation, symptom control and promoting patient comfort and well-being (Lavery 2000, Naylor et al 2001).

8.1.3 Patients may also present having had previous radiotherapy with associated ischaemic tissue, complicated by the presence of a FBW. These patients present a particular challenge.

8.4 Staging of breast cancer

The American Joint Committee on Cancer (2001) restaged Fungating Breast Cancer from T3 to T4, where care is defined as being aimed at symptom control rather than curative treatment. Subsequently an additional revision (AJCC 2002) has characterised metastatic disease (T4) in more detail (Ta-Td) (Thor 2004, SIGN 2005b).

9.0 Patient Assessment

There are a number of areas that need to be assessed in patients with FBW; these will include those outlined in Table 1.

Table 1: Patient Assessment

Clinical /Social History Cause and stage of disease Treatment and progress Patient and family knowledge of the diagnosis Nutritional Assessment Psychological impact of the Wound Impact of the wound on Quality of Life Resources available Social Support network Patient and caregiver education
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(Morison et al 1997, Flanagan 1997, Seaman 2006)

Whilst the importance of a MDT approach has been previously identified it must also be recognised that the patient may want to limit the number of health care professionals who are required to provide direct care. Therefore this aspect must be taken into account in the overall management of the patient.

9.1 Presenting Symptoms

A review of the literature has established that the symptoms experienced by patients are multifaceted and distressing (Naylor 2002a {Table 2}, Dowsett 2002, Wilson 2005, Seaman 2006). In addition each patient and their wound are unique in terms of their presentation and symptoms (Barton and Parslow 2001, Young 2005). Morison et al (1997) suggest that the 'problems' identified establish the knowledge base that professionals require to care for patients with FBW.

Table 2: Common physical and psychosocial problems:

Wound Related	Psychosocial
Location	Body Image
Size / Shape	Communication
Excessive exudate	Cosmesis of dressing
Unpleasant odour	Denial
Pain – dressing / wound / disease related	Depression
Bleeding	Embarrassment
Infection	Fear
Devitalised tissue	Guilt
Comfort of dressings	Impact on family
Frequency of dressing change	Information Needs
Poor skin integrity	Restrictions (due to dressings)
Surrounding skin - Pruritis	Revulsion / disgust

The wound is often difficult to disguise	Self-Respect / Self-esteem Sexuality Shame Social Isolation Social Support /Resources
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Naylor W (2002a) Part 1: Symptom control in the management of fungating wounds. <http://www.worldwidewounds.com/2002/march/Naylor/Symptom-Control-Fungating-Wounds.html>

These fungating breast wounds are often hidden from family until breast cancer is advanced and terminal. There may have been much secrecy causing many psychosocial problems. This inhibits quality of life and open discussion with loved ones. The patient may experience multiple symptoms (Naylor, Laverty and Mallett 2001, Barton and Parslow 2001) with problems that are often recurring and require sometimes inventive approaches (Carville 1995, Young 1997b). Fletcher (2007) provides a useful guide to dressing awkward areas that may assist the practitioner in utilising the best approach. Assessment should include consideration of these and management should be modified to meet the individual needs of the patient. The subsequent dressing regime needs to be such that both trained and untrained carers can manage the procedure.

Whilst lymphoedema of the arm is a common complication normally associated with treatment of breast cancer (Pain and Purushotham 2000, Soran et al 2006), patients with FBW may present with lymphoedema as a consequence of the tumour blocking the axillary vessels. Therefore practitioners need to be able to manage this symptom in conjunction with other physical problems.

In addition to the physical symptoms there are psychological effects that also require careful attention (Naylor 2002a, Young 2005). Grocott, Browne and Cowley (2005) highlight the findings of Lawton (2000) who undertook an ethnographic study in hospice setting. She identified a theme she termed 'social death' which seemed to occur prior to 'physical death', which draws attention to the complexity of the situation and the impact of social isolation.

9.2 Wound Assessment

Wound assessment should include an evaluation of; site, location, surface area – where the wound is close to the axilla it can affect movement of the joint or ability to fix a dressing (Collier 2000). Measurement of the size will help to determine the size of dressing required. The type of tissue (i.e. slough, necrosis, signs of infection) and percentage of devitalised tissue (Collier 1997, Collier 2000). The amount and type of exudate, depth of the wound (to include assessment for sinus or fistulae), presence of odour, history of bleeding and pain all need to be assessed. Furthermore the surrounding skin will need to be observed for signs of maceration, excoriation or fragility (Collier 2000, Bates-Jensen, Early and Seaman 2001, Seaman 2006).

A system of note-taking has been developed (TELER) that can assist the practitioner in assessing the wound and provide a means of planning patient centred treatment goals (Grocott 1997, Grocott 1998, Grocott and Cowley 2001), expressed in terms relevant to the patient. Table 3 provides an example of TELER codes for the evaluation of exudate leakage.

Table 3: Example of TELER codes for exudate leakage

CODE	DESCRIPTION
5	Dressing only is soiled
4	Dressing only is sodden

3	Dressing is wet and bedding and clothes are soiled
2	Dressing is wet and bedding / clothes are wet
1	Dressing and bedding / clothes are soaked
0	Dressing is stained in patches, bedding / clothes are soaked

Grocott P and Cowley S (2001) The palliative management of fungating wounds – generalising from multiple-case study data using a system of reasoning. *International Journal of Nursing Studies*, 38, 533-545

However there is continued debate about such specific tools and patient self assessment tools such as WoSSAC (Naylor 2002b) which rates the severity of symptoms and interference on everyday activities. The authors highlight the advantages / disadvantages of each, however without further studies to validate these tools it is difficult to draw firm conclusions (Naylor 2002b, Grocott, Browne and Cowley 2005).

There are examples of more generic wound assessment tools such as the WHRU Assessment Form (Wound Healing Research Unit 2001) and those specific to pressure ulcers PSST (Bates-Jensen, 1995, 1997) and PUSH (PUSH Tool 3.0, NPUAP 1998). These tools could be adapted to suit the needs of patients with FBW and furthermore aid the practitioner in making an accurate assessment.

9.3 Pain Assessment

Tissue hypoxia and necrosis occurs as part of the progression of the malignant process, meaning that patients may experience various types of pain or discomfort (Naylor 2001b, Barton and Parslow 2001). Therefore it is important to identify whether the pain is related to the disease i.e. tumour progression, the wound or both (Naylor, Lavery and Mallett 2001, Seaman 2006). Pain can be related to other elements than the disease process, this may include maceration and excoriation from excess exudate levels.

There are a number of validated pain assessment tools that can be used as part of the assessment process; however the practitioner should be aware that not all may be able to differentiate between the various factors that contribute to the overall pain experienced. In addition practitioners should be able to differentiate between the various types of pain, such as nociceptive and neuropathic (Naylor 2001b, Dowsett 2002) to ensure the appropriate management. Pain assessment should be carried out during dressing procedures as well as pre and post to fully appreciate the impact (Dowsett 2002). Table 4 outlines the aspects of pain that need to be assessed and also lists some of the various tools available.

Table 4: Pain Assessment

Pain Assessment	Assessment Tools
Location	Visual Analogue Scale (VAS)
Nature	Vertical VAS
Severity	Numerical VAS (with divisions)
Onset	Descriptive rating Scale
Frequency	Faces rating scale
Duration	
Aggravating Factors	
Alleviating Factors	
Impact on Activities of Daily Living	
Current Analgesia	
Effectiveness of treatment	

Naylor W (2001b) Assessment and management of pain in fungating wounds. *British Journal of Nursing (Supplement)* 10,22,S33-S52

10. Goals of Management:

Grocott (2002) suggests that management should include treatment of the underlying tumour, symptom control, local wound management as well as supportive care to the patient and their family. The concepts regarding management have been drawn from areas of oncology, chronic wound care and palliative care (Grocott 2007a).

The management plan may also include radiotherapy, chemotherapy and hormone therapy as well as more local topical wound treatments to palliate the symptoms (Hallett 1995, Haisfield-Wolfe and Rund 1997, Miller 1998, Naylor, Lavery and Mallett 2001, Seaman 2006). None of the interventions are a cure for advanced cancers however they may extend the patients life, ease the pain and bleeding and improve some aspects of quality of life (Seaman 2006). However the side effects of each have to be considered and balanced with the potential benefits (Morison et al 1997, Grocott 2007a).

Previous authors suggest that the aims of management include minimisation or containment of symptoms (Naylor, Lavery and Mallett 2001) where healing is not usually an achievable outcome (Goldberg and McGinn-Byer 2000, Hampton 2004, Maund 2008) and curative intent is no longer appropriate or effective (Bale and Jones 2006). Table 5 outlines some of the considerations in terms of management.

Table 5: Objectives of management may include

To decrease malodour
To manage exudate
Control pain
Maintain integrity of surrounding skin
Control surface bleeding
Improve quality of life
Overall palliation not healing

(Collier 2000, Wilson 2005, Seaman 2006, Langemo et al 2007).

Naylor (2002a) concurs with previous authors but also adds additional aims of patient comfort, confidence in the professionals providing care and a sense of well-being to maintain or improve their quality of life.

Ultimately there is a reliance on the appropriate dressing being selected, the effectiveness of which should be measured by their ability to meet the required outcome, and will include measures other than 'healing'. Practitioners must take into account problems as perceived by the patient (Collier 2000) as they are key to judging the effectiveness of treatments (Naylor, Lavery and Mallett 2001). Grocott (2007a) identifies additional skills that the practitioner may need, to include stoma and continence care, as well as being aware of appropriate nutritional intervention and pain relief measures. There is an existing range of guidelines available to help guide assessment and management (Twycross et al 2002, SIGN 2005ba, SIGN 2005b, SCHIN 2006).

10.1 Aspects of Management

10.2 Wound Cleansing

Generally normal saline is the solution of choice (Collier 2000, Draper 2005), although showering may be appropriate if the patient's wishes and can manage this (Wilson 2005, Draper 2005). Whichever method is chosen the fluid should be warm (Langemo et al 2007) and the procedure should be carried out gently so as not to risk bleeding (Seaman 2006). It is also advisable to

avoid swabbing the wound as this may also cause damage and risk haemorrhage. Generally topical antiseptics should be avoided because they can cause local reactions and are ultimately inactivated by the devitalised tissue present in FBW (Draper 2005).

10.3 Malodour

It is commonly recognised that offensive odour is a major problem for patients with FBW, it is very distressing and can lead to additional problems of nausea and subsequent loss of appetite (Moody 1998). Ultimately the patient may become socially isolated due to concerns of others being able to smell the wound (Van Toller 1994, Piggin 2003). It is important to try and establish the cause of malodour (Lazelle-Ali 2007) however the difficulties of measuring 'smell' have been highlighted (Clark 2002). The assessment of odour should be carried out from the patient's rather than the professional's perspective (Morison et al 1997, Dowsett 2002).

There are existing measurement tools such as TELER to help to objectively assess the level of malodour (Grocott 1997, Browne et al 2004). This not only takes into account the level of perceived odour but in addition acknowledges social factors. However existing studies are very few making generalisations difficult.

Such unpleasant odour is generally caused by the type of tissue present, which is often sloughy or necrotic. The presence of this devitalised tissue can lead to the growth of aerobic and anaerobic bacteria which in turn can lead to infection (Hampson 1998, Naylor 2001 Seaman 2006). In addition to the type of tissue odour may also be due to the presence of stagnant exudate (Collier 2000, Barton and Parslow 2001, Draper 2005), hence the need for adequate wound cleansing and timely dressing changes (Draper 2005, Langemo et al 2007). Table 6 outlines the main forms of management.

Table 6: Management of Malodour

systemic metronidazole topical metronidazole and /or antimicrobials charcoal dressings

Draper C (2005) The management of malodour and exudate in fungating wounds. British Journal of Nursing (Tissue Viability Supplement). 14,11, S4-S12

In addition to local wound management interventions such as those listed above, Ferris and von Gunten (2001) have suggested that odour absorbers such as cat litter or activated charcoal placed under the bed of the patient may also be an effective method of reducing odour.

If malodour is associated with clinical infection then the patient will require systemic antibiotics (Thomas et al 1998, Wilson 2005, Seaman 2006). Guidelines suggest that oral metronidazole 400mgs three times daily for 2 weeks is appropriate (CREST 1998, SCHIN 2006) however patients may experience gastric disturbances and not be able to tolerate this. An alternative regime of 200mgs twice daily may be considered to be for maintenance purposes and reduces the unpleasant side effects and rectal administration may also be indicated (SCHIN 2006).

Topical metronidazole (TM) can also be used, a method delivery which avoids effects such as nausea or vomiting (SCHIN 2006). Thomas and Hay (1991) have suggested that 0.8% TM is active against a range of microorganisms that may be implicated in such wound types. In a later study by Finlay et al (1996) 0.75% TM was used in a sample of 47 patients with a variety of malodorous benign and malignant lesions. No placebo treatment was included because of the ethical issues of not treating malodour raised by the authors. Their findings indicated that by day fourteen 95% (n=41) reported a decrease in smell. The study also outlined that topical administration is a more expensive treatment than oral. Unfortunately there is no sub-group analysis to examine the effects of treatment for patients with FW.

To date there is still debate about the optimal dose of metronidazole (Draper 2005, Lazelle-Ali 2007) however previous research has suggested that 1g of metronidazole is required per cm² (Bower et al 1992). This dosage would be applied to the wound surface once or twice daily following wound cleansing and is usually effective in 2-3 days (Draper 2005, SCHIN 2006) with the length of treatment being 5-7 days (Naylor, Laverty and Mallett 2001). However current evidence is based on small studies making generalisations difficult. Furthermore it has been suggested that largely exuding wounds can make the gel ineffective by diluting the concentration (Grocott 1999). Also practitioners need to consider that the use of TM can exacerbate the problem of exudate management. Clark (2002) suggests that further studies into its effectiveness are required.

11. Use of Dressings

Grocott (2002) undertook a review of the key published work from 1991-2001 regarding the management of FW, she concluded that the numbers of studies remains small. Some of the judgements made were that the use of metronidazole still needs further research, dressing usage needs additional evaluation and objective patient / wound assessment tools require more investigation.

More recently Adderley and Smith (2007) undertook a systematic review of topical agents and dressings for FW; however they were unable to provide any conclusive evidence of the role of many of the topical products that are used in the day-to-day management of patients. This was related to methodological considerations that precluded certain levels of evidence. Therefore they suggested that further research is required to establish guidance for practice.

There is a general acceptance that many of the wound dressings currently available are appropriate to use in the management of patients with FBW. The guiding principle of modern wound management being based Winter's work on moist wound healing in the 1960's (Harding et al 2000, Cutting and White 2002). This is based on beliefs that the wound healing process generally requires such an environment for cells to work effectively (Jones et al 2006). However whilst there are hundreds of research studies that have examined the myriad of products in a variety of wound types the inclusion of patients with FBW in such trials are minimal.

Recently experts in the management of patients with FW have questioned confidence in the principle of moist wound healing (Grocott and Cowley 2001, Grocott 2007a, 2007b) as the management of excess moisture is in fact a challenge which potentially requires an alternative theoretical framework. Recent developments such as the WRAP collaboration are attempting to bridge this gap (Browne, Grocott, Cowley et al 2004). Such progress has the potential to have an impact on other groups of patients where exudate management is an issue.

Generally the criteria on which to base dressing choice are:

- Tissue involved
- State of healing
- Aetiology of the wound
- Condition of the wound
- Environment and Carer
- Healthcare System

Harding et al (2000)

In addition whilst concepts such as Wound Bed Preparation (WBP) may be appropriate for healing wounds, the aims for patients with FBW are different (Grocott 2007a). Table 7 outlines the principles of wound bed preparation according to Grocott (2007a).

Table 7: Principles of wound bed preparation for FW

Wound Bed Preparation for Fungating Wounds
Control odour
Control pain
Control bleeding (Trauma free dressing change)
Debride dead tissue (unless a natural scab is indicated)
Decrease bacterial overload and odour
Manage exudate by evaporating excess fluid
Protect peri-wound skin from excoriation / maceration
Prevent soiling
Curb frequency of dressing change

Grocott P (2007a) Care of patients with fungating malignant wounds. *Nursing Standard*. 21, 24, 57-66

In addition practitioners need to consider issues of re-establishing body symmetry and the cosmetic acceptability of the dressing to the patient (Grocott 1995a, 2000a).

Whereas generally the principle consideration when choosing a dressing is efficacy, attention to local availability, number of applications, complexity of procedure and additional patient care needs also need to be thought about (Goldberg and McGinn-Byer 2000). Dowsett (2002) suggests that practitioners need to be flexible in their approach, taking into account the patient's concerns as the main focus. See Appendix 1, Table 1 which outlines the current dressings available (BNF 2007). Consideration also needs to be given dressings included in the Drug Tariff as not all the dressings are available in the community. This often presents a challenge to community practitioners who then find it difficult to obtain the most appropriate products.

11.1 Dressings for the management of malodour

11.1.1 Charcoal Dressings

Such dressings usually contain activated charcoal which acts as a filter to adsorb volatile chemicals. However their ability to maintain this effect relies on them not getting wet (Draper 2005), therefore frequent dressing changes may be required. The practitioner also needs to be aware that whilst some charcoal dressings can be cut to size others should not be (Wilson 2005, Draper 2005, Seaman 2006). One of the difficulties is finding a large enough dressing to cover the wound and contain the exudate (Lazelle-Ali 2007).

11.1.2 Silver

Silver is known to be antibacterial (Demling and DeSanti 2001 Thomas and McCubbin 2003) and when combined with charcoal can help with deodorising in addition to its antimicrobial action (Draper 2005). However there are no studies that compare the effectiveness of activated charcoal dressings with silver and plain charcoal to draw any firm conclusions in relation to FBW (Draper 2005). Furthermore, dressings that contain hydrofibre or foam technology in combination with silver can have a substantial capacity to absorb large amounts of exudate. These can also be cut to size.

11.1.3 Foams

There a number of foam dressings that have the ability to absorb large amounts of exudate. These have also now been combined with silver to have an added antimicrobial benefit. They can be left in place for longer periods of time, depending on the amount of exudate. They also have

the ability to vent moisture away from the wound bed, although the risk of maceration may only be avoided with frequent dressing changes.

11.1.4 Combination dressings

There are dressings available that combine the benefits of charcoal and hydrofibre or silver and foam as well as low-adherence, however it is often the amount of dressings required that influences the final choice.

11.1.5 Honey and Yogurt

Whilst there are reports of honey being used because of its antibacterial action (Wilson 2005), caution must be employed in view of its additional debriding action where bleeding may result. A review of the literature established use in FBW is not common practice.

11.2 Management of Exudate

Whilst in normal wound healing exudate can assist healing, its presence in excessive amounts can prevent or delay wound healing ((WUWHS 2007). FBW often produce moderate to large amounts of exudate, this in part due to the increased permeability of vessels in the tumour (Haisfield-Wolfe and Rund 1997) although the presence of infection and associated bacterial enzymes may also be implicated (Naylor 2002a). Current guidance suggests that practitioners should aim to assess all the factors that may be contributing to exudate formation and evaluate the interaction between this and dressing performance (WUWHS 2007).

Uncontrolled exudate can lead to soiling of dressings and clothing, peri-wound maceration and odour (Draper 2005, Grocott 2007a). Therefore the aim of management should be to conceal and collect the exudate produced (Seaman 2006), as well as achieve an acceptable cosmetic effect (Naylor, Laverty and Mallett 2001). Grocott (2007a) also suggests that exudate control can help patients regain control over their lives as this often the most limiting and debilitating symptom.

For moderate to heavy exudate a number of dressing products can be used, to include; alginates; hydrofibre; and foams (Draper 2005).

11.2.1 Alginates

There are two distinct types that absorb different amounts of exudate. Some are classified as haemostatic alginates and therefore can assist arrest minor bleeding. They are available in flat sheets and ribbon so are able to conform to the shape of a wound so can be useful for awkward shaped wounds. The composition of the dressing is such that the fibres are designed to breakdown; however the dressings rely on exudate being present to do this. Therefore if the wound is dry alginates should be avoided as they may adhere and cause trauma on removal (Jones et al 2006).

11.2.2 Hydrofibre

As previously stated these have been shown to absorb large amounts of exudate with the additional benefit of limiting the risk of maceration by vertical wicking. The dressing is available with added silver and is produced as flat sheets and ribbon, which is useful for conforming to cavities. The dressing maintains its integrity reducing the risk of fibres being incorporated into the wound.

Both hydrofibre and alginate dressings need to be secured by a secondary dressing to prevent leakage.

11.2.3 Foams

These dressings are available as polyurethane foam or silicone foam. Their properties are such that they transmit moisture vapour and oxygen and provide thermal insulation (Jones et al 2006). There is a wide range of dressings of this type which have varying absorbencies. They are available in a variety of sizes and some are designed for use in cavity wounds.

Currently there is a best practice statement available that provides a consensus based on expert opinion with regards to the role of exudate, its assessment and management (WUWHS 2007). Therefore practitioners should be encouraged to use this as a resource.

11.2.4 Prevention of Trauma

There is a risk of bleeding if any of the dressing types adhere to the wound bed. Therefore the dressing will need to be soaked off to prevent the risk of bleeding. In view of this adhesive dressings and those that contain petroleum should be avoided.

Grocott (2000a, 2000b) evaluated a number of dressing regimes for the management of exudate and has suggested the following:

- 2 layer permeable system – which comprises a non-adherent contact layer and an absorbent outer layer
- 2 layer controlled permeability – highly absorbent alginate /hydrofibre and a secondary foam dressing with a high MVTR.

Grocott (2000a, 2000b) highlights that currently the range of dressing sizes currently available does not meet the requirements of patients with FBW. In addition manufacturers need to consider how the MVTR can be improved.

Where dressings are being changed frequently and the wound shape allows practitioners may want to consider the use of stoma products to assist with exudate management.

11.2.5 Stoma appliances / Wound Managers

The use of ostomy products, ointments and skin sealants may be appropriate as an alternative to dressings where exudate management is of paramount importance. If the wound is small then stoma bags can be used, therefore referral to a stoma nurse may be appropriate. If however the wound is larger and the dressing is being changed 2 – 3 times per day then alternative pouches may be an option, again liaison with stoma therapists is advisable. At present there are no studies examining the effectiveness of this system for patients with FBW.

Grocott (2007b) suggested that it may be preferable to promote the formation of a natural scab in patients with FBW, which may in turn reduce the levels of exudate and perhaps the risk of bleeding occurring from traumatic injury. Although products that address this issue are not widely available, some manufacturers are evaluating the use of materials that may enhance this process.

11.3 Management of Maceration

Maceration is a common problem and is linked to the amount of exudate produced. Inadequate management can lead to further skin breakdown and enlargement of the wound (Cutting and White 2002). Therefore dressings that absorb exudate are of paramount importance (see

previous section – Management of Exudate). Practitioners must be able to gauge the most appropriate dressing based on the proposed characteristics (Cutting and White 2002).

In conjunction with exudate management the surrounding skin requires protection, products known as 'barrier films' or 'barrier creams' are most commonly used. These should be alcohol free to avoid further stinging or discomfort. In addition to their barrier function they can also help to provide a surface to which tapes and adhesives can adhere (Wilson 2005).

11.4 Management of Surrounding Skin

The peri-wound area can be extremely fragile due to a number of reasons (Seaman 2006); the patient may have had previous radiation, or there may be an ongoing inflammation due to the tumour, adhesive dressings can cause skin stripping or there may be maceration from uncontrolled exudate. Therefore barrier films should be used for protection, adhesive products should generally be avoided, however thin hydrocolloids or semi-permeable films may help to protect vulnerable skin if used in conjunction with a barrier (Cutting and White 2002, Draper 2005).

Patients may also report pruritis or itching which may be related to excoriation; therefore prevention is preferable, with the use of skin barriers (Naylor, Lavery and Mallett 2001). However progression of the tumour should also be considered as a cause of itching and irritation (Twycross et al 2002). If there are signs of infection, the practitioner should consider both bacterial and fungal origins (Goldberg and McGinn-Byer 2000) and treat accordingly.

Beynon, Lavery, Baxter et al (2003) have reported on the use of a thermoreversible gel which was used on a small sample of patients as a barrier to prevent excoriation. The gel seemed to ameliorate soreness (as measured using a TELER scale) in patients with gynaecological related malignancies. However the authors suggest that further research comparing this with other skin barriers is required before any recommendations can be made.

11.5 Management of bleeding

Patients may be at risk of bleeding due to coagulation defects as a consequence of cancer and its treatment or from progression of the disease. Some lesions have the potential to erode into major blood vessels therefore careful planning is required (Barton and Parslow 2001). In addition the wound bed can be extremely delicate; one of the main ways of reducing the risk of bleeding is by careful dressing changes that minimise trauma (Wilson 2005, Seaman 2006, SCHIN 2006). Therefore practitioners must avoid inappropriate dressing choices. The patient can be prone to acute or chronic anaemia if bleeding presents as a problem so consideration should be given as to the most appropriate treatment.

A number of treatments can be employed depending on the degree of bleeding:

- Initial first aid may be through applying compression to the area (Naylor, Lavery and Mallett 2001, Seaman 2006), or if severe adrenaline can be used under close medical supervision in an emergency situation.
- For minimal bleeding, silver nitrate can be applied to bleeding points (Seaman 2006) (although this can cause minor irritation). Haemostatic alginates can also be used (Seaman 2006).
- The patient may require radiotherapy treatment as this has the effect of occluding small vessels which decreases neovascularisation and may help to decrease exudate levels as well as ameliorate pain and bleeding (Bale and Jones 2006).

11.5.1 Role of wound debridement

Many of the authors reviewed discuss the role of debridement (Naylor, Lavery and Mallett 2001, Draper 2005, Wilson, Seaman, Langemo et al 2007). However only a few debate the risks of different methods of debridement in terms of the risk of bleeding or haemorrhage. Most agree that surgical debridement is not an option and advocate gentle debridement. Grocott (2007a) suggests that there is a potential role for autolytic debridement, however there should be judicious assessment of the clinical benefit of removing dead tissue.

Methods that are considered inappropriate for debridement are:

- larvae,
- enzymes
- surgical / sharp

This is because of the risk of bleeding (SCHIN 2006). Therefore clear guidance is required for practitioners if risks to the patient are to be minimised.

11.5.2 Silicone Dressings

This type of dressing can reduce the risk of bleeding and pain associated with dressing removal when tissue is very friable and fragile. This type of dressing is normally coated with a non-adherent surface which helps to keep the dressing in place, and also allows exudate to pass through. The advantage of using this is that it is kept in place for 6-7 days with the secondary dressing being changed as required.

12. Management of Pain

12.1 The World Health Organisation have suggested an analgesic ladder (WHO 1996) therefore this should be considered when attempting to plan the appropriate intervention for pain relief (Naylor 2001, SIGN 2005a). There is a well established role for opiates in the management of pain, which can be administered orally, intravenously and intra-muscularly.

12.2 In addition topical application has been used (Back and Finlay 1995, Krajnik and Zyllicz 1997). These studies have suggested that 10mgs of diamorphine in 15g of a hydrogel can help to some degree. Topical applications should be administered once or twice a day (SCHIN 2006); however the duration of treatment has not been clearly identified to date. A disadvantage of using a hydrogel carrier is that they are 70-90% water-based therefore fluid handling can be a problem which has the potential to exacerbate maceration.

12.3 Zeppetella and colleagues have examined the analgesic efficacy and bioavailability of topical morphine in patients with 'painful ulcers' (mainly pressure ulcers) and found a reduction in VAS scores (Zeppetella, Paul and Ribeiro 2003). It works by local mediation of pain relief, rather than systemic absorption (Ribiero, Joel and Zeppetella 2004). Furthermore they examined the stability of morphine prepared in advance and stored under different conditions (Zeppetella, Joel and Ribiero 2005). They concluded that morphine was stable for 28 days if prepared in a sterile environment; however it should be used within 7 days if not sterile.

12.4 MacGregor et al (1994) examined the use of a local anaesthetic gel for analgesia to treat pain experienced from skin excoriation, although in a review of the current literature there is limited further evidence of the use of this.

- 12.5 Although approved for the use on patients with postherpetic neuralgia pain (Popescu and Salcido 2004, DTB 2008) the use of lidocaine as a patch or a solution has been reported in the management of patients with acute and chronic wounds. The use of Lidocaine solution has been previously reported as a topical method of pain relief at dressing change (Krasner 2002, Doughty 2006), allowing 15-20 minutes before then changing the dressing or undertaking debridement. Davis and Adams (2006) report using a topical 5% lidocaine patch in the management of local pain associated with leg ulcers (although the aetiology is not stated), whilst Lockhart (2006) reports the use of lidocaine 10% patches on surgical wounds post –operatively with good effect. However there is limited evidence to support its use as a patch or solution for patients with FBW.
- 12.6 Previous authors have discussed the use of local anaesthetic creams as a method of reducing pain prior to debridement of a wound (Krasner 2002, Popescu and Salcido 2004). A review of topical agents for pain in venous leg ulcers suggests that such creams applied 30-45 minutes before wound debridement may provide some pain relief (Briggs and Nelson 1999). Whilst previous authors have called for further research into its effects on wound healing (Popescu and Salcido 2004) it must be remembered that for patients with FBW healing is not usually a priority. Therefore it may be appropriate to re-examine the use in this particular patient population.
- 12.5 Adjuvant analgesics such as anti-depressants, anti-convulsants, non-steroidal anti-inflammatories (NSAIDS) and steroids may also be required to treat pain. It has also been suggested that Entonox can be used pre / peri dressing change (Evans 2003), although the evidence for its effect in wound management procedures is limited (Naylor, Lavery and Mallett 2001). Furthermore it is not available in the community setting where most patients are cared for.
- 12.6 As well as pharmacological interventions, non-pharmacological measures should also be considered (Naylor 2001). These will include wound cleansing technique, choice of wound dressing and protection of the surrounding skin. Thus the importance of an accurate assessment of the patient and their wound cannot be over emphasised.
- 12.7 Recently hydrogel sheets have been reported as providing a topical means of pain relief (Young and Hampton 2005, Maund 2008).
- 12.8 Although not reported for use on patients with FBW, a recent advancement of a foam dressing with added Ibuprofen has been reported as decreasing wound pain in patients with venous leg ulcers (Jorgensen et al 2006, Sibbald et al 2007, Gottrup et al 2007). Therefore further research into its use on patients with FBW should be evaluated.

13. Communication

- 13.1 Establishing a good relationship with the patient, family and / or carers is very important. The practitioner needs to show compassion, and be able to reduce any anxieties. What is of equal importance is to try and maintain a consistent team of individuals to care for the patient (Wilson 2005). The patient should feel able to communicate their problems to the practitioner and feel able to contribute to a management plan that takes into account their problems.

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15. Appendix 1

Table 1 Current generic groups of dressings available (BNF 2007).

GENERIC GROUP
<p>Alginates</p> <p>Calcium Alginates</p> <p>Alginate with hydrocolloid</p> <p>Calcium Alginate (with silver)</p> <p>Calcium Alginate (with honey)</p>
<p>Foams</p> <p>Polyurethane Foam</p> <p>Polyurethane Foam Film with adhesive border</p> <p>Polyurethane Foam Film without adhesive border</p> <p>Foams with silver</p>
<p>Hydrogels</p> <p>With alginate</p> <p>With honey</p>
<p>Hydrocolloids</p> <p>Potentially used as a border for FW</p> <p>Hydrocolloid and Alginate with silver</p> <p>Hydrocolloid Fibre</p> <p>Hydrocolloid Fibre with silver</p> <p>Hydrocolloid with silver</p>
<p>Low Adherent</p> <p>With silver</p>

Odour Absorbent with silver
Odour Absorbent
Skin Protectives
Surgical Absorbents
Topical Metronidazole

Any dressing should be removed with caution in case of adherence to the wound bed which might precipitate bleeding.

Appendix C – Position paper. Some views on the role of chemotherapy, hormone therapy, radiation treatment and biological therapy

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Introduction

Locally advanced breast cancer accounts for between 5-30% of all cases depending on the study population (1, 2). In western communities, it accounts for less than 5% of screen detected patients (3).

Historically there was no standard definition of locally advanced breast cancer (LABC) the term being generally applied to those cases felt to be inoperable. It is now seen to cover a broad variety of clinical presentations:

- A large primary tumour greater than 5cm (T3).
- Skin or chest wall involvement (T4).
- And/or fixed axillary (N2) or ipsilateral internal mammary lymph node involvement (N3).

This corresponds to Stage IIIa (T0-2N2 or T3N1-2) and stage IIIb (T4N0-2) and IIIc disease (any T1N3). (AJCC) (4).

In the 2006 TNM revision, ipsilateral lymph node metastasis was reclassified as LABC and such patients were not included in studies of LABC before this and needs to be borne in mind when interpreting modern results. Such patients have a survival closer to Stage III B than IV disease (5-7).

Inflammatory breast cancer (T4d) is included in most classifications.

The results of treatment, of locally advanced breast cancer have been poor with five year survival rates as low as 30% in some series (8-10).

Primary Inflammatory breast cancer occurs in 0.5-2% of cases, with a median survival of 2.9 years compared to 6.4 years for non-inflammatory LABC (11).

Modern treatment employs a multi-modality approach of chemotherapy, surgery, radiotherapy, hormone therapy and more recently the introduction of biological therapy. This paper will explore the role of each in the management of LABC and provide a discussion document for the NICE breast panel.

Problems in interpreting trial results

Chemotherapy, surgery, radiotherapy, hormonal and more recently targeted therapies have been given in many different combinations and sequences. Progress has been limited by the relative infrequency of the disease and because of this the difficulty in developing large sized and meaningful randomized phase III trials in LABC (12).

The majority of the data guiding treatment comes from phase II studies often with small numbers

of patients or retrospective reviews of single institution experience, with only a few randomized trials having been carried out (13-16). Neoadjuvant chemotherapy is included in breast cancer treatment guidelines but this is not based on the results of large randomized trials. Indeed few drugs detail their use in the neo-adjuvant setting in their licensed indications.

Clinical response is the most universal measured of drug efficacy. The WHO/UICC criteria have been applied for 20 years (17) but RECIST (Response Evaluation Criteria) in solid tumours (18,19) has been used in more modern times. A CR is the same in both systems but a PR is defined as a 30% disease in the largest tumour dimension in the RECIST system and needs to be recognised when reviewing recent studies.

Studies have variable stage mix at presentation which may contribute to the wide variations of response rates seen (47-100%) (20-39).

Clinical responses (CR) can be difficult to define from one study to another but pathological complete response (pCR) is the most powerful predictor of clinical outcome in terms of survival (40-42). Unfortunately there are different systems for assessing pathological response making cross study comparisons difficult. (3, 43-49).

Indeed in most trials pCR refers to the response in the breast, not the response to primary chemotherapy which has occurred in the regional lymph nodes.

However the 2006 Consensus stated that for a pCR there must be no histological evidence of residual tumour cells, either in the breast or axillary nodes – a pCR is excluded if non-invasive tumour cells are found (50). It remains to be seen how well this will be adopted outside America. However irrespective of the criteria applied patients who achieve a pCR have a better outcome (81, 152).

On a parallel front in recent years pre-operative systemic therapy (PST) has been used increasingly in otherwise operable stage I and II cases aiming at greater rates of breast conservation. This will provide more rapid efficacy assessments of new drug regimes due to the greater number of cases. However how well these relatively early cases inform the treatment of LABC remains to be seen (51).

Predictive Factors

When considering systemic treatment the most useful predictor for response is the ER/PR status. Whilst confirming the potential benefit for hormone therapy in elderly patients higher pCRs have been seen in tumours not expressing steroid hormone receptors (52-54).

No single molecular histological or biological marker reliably predicts benefit from chemotherapy. The oncoTYPE DX assay, a 16 breast cancer gene expression assay, is commercially available but has yet to be validated in prospective randomized trials. Studies are underway to investigate gene panels (TAILORx Trial, MINDACT Trial) but at this point these approaches are investigational and do not form part of routine practice.

Chemotherapy

In the early 1980s, neoadjuvant chemotherapy was introduced in patients with locally advanced breast cancer, (55-61).

Results from non-randomised studies of primary systemic chemotherapy given pre-operatively show complete clinical responses ranging from 10% to 63% (20-39) of which only 50% to 66%

are pathologically confirmed (pCRs), the overall pCR rate ranging from 3.5 to 30% (5, 20-40, 62-66, 76-80).

Neo-adjuvant chemotherapy converts clinically positive nodes to negative nodes in 23-38% of patients with LABC (refs 67-69). Clinical response to neo-adjuvant treatment and in particular complete pathological response are predictors of subsequent outcome. Pathological involvement of axillary nodes following neoadjuvant therapy portends a poor prognosis.

Patients with negative nodes have a better outlook.

Several studies have shown a correlation between chemotherapy response, residual tumour in the breast and axilla and RFS and OS (64, 70-75)

Analysis of these studies shows improved DFS and OS in patients who achieve a pCR compared to those who do not and hence stimulating studies to increase the pCR rate.

Ongoing studies are investigating whether induction regimens that substantially increase pCR rate can improve DFS and OS and if pathologic response can guide post-operative chemotherapy (70, 74)

As a result of the observed response rates the possibility of Breast Conserving Surgery (BCS) in patients with large operable primaries has led to the increasing introduction of neoadjuvant chemotherapy in this group of patients.(23,26,27,29,31,32,40,64,74,75,80,88,89).A study comparing BCS v mastectomy in LABC was abandoned because of poor accrual(279). In studies of pre-op v post op chemotherapy there has been an increase in BCS and no survival difference (81-84).

A meta-analysis of nine trials randomly assigning women to adjuvant or neo-adjuvant chemotherapy have not shown any survival advantage (85).

Neoadjuvant systemic treatment is therefore, in this group of patients, considered as safe and effective as the same treatment administered post-operatively (85).

The results of chemotherapy with metastatic breast cancer and axillary node positive disease have demonstrated the superiority of anthracycline containing combination chemotherapy over CMF (280-283). On this basis and the good response rates from neoadjuvant phase II studies the general consensus is to recommend an anthracycline based regimen unless there is a contraindication (50, 90-92).

Commonly used schedules are AC, CAF, FAC, (23, 26, 35-36, 93) FEC, (39, 93-95) Ax4 + CMF (96) and multi drug regimens (32, 97). Non anthracycline based regimes should be used for patients with significant cardiac histories but there is no data to give a recommendation for a particular schedule.

Taxanes have been shown to have significant antitumour activity as first and second line treatment in metastatic breast cancer even with patients anthracycline resistant disease (98-102).

Anthracycline/Taxane based chemotherapy based regimens have been tested extensively with pCR rates of 15-30%, combinations include AC followed by paclitaxel or docetaxel/docetaxel doxorubicin cyclophosphamide/epirubicin-paclitaxel followed by CMF and dose dense epirubicin and paclitaxel. (103).

Strategies have included sequential use, concurrent with other agents,(usually anthracyclines) and both sequential and and dose dense schedules in operable breast cancer. Many of the studies are small or have only been published in abstract form. (104-148) Treatment with paclitaxel in dose dense and weekly schedules appears promising. (149-151).

Docetaxel seems less schedule dependent and has yielded pCRs up to 30% (50, 103).

Many of the studies are not yet mature and disease free and overall survival data are sparse. The Aberdeen trial (11) showed an improvement in pCR, DFS and OS but used a non-standard regimen as the control arm (CVAPx8), the numbers were small and the pathology has not been independently reviewed. The NSABP B-27 study has not shown any survival advantage so far. (152).

In the absence of survival data, pCR and clinical complete response may serve as surrogates for survival. Three trials have shown improved complete and/or partial pathological responses with the addition of a taxane to a neoadjuvant anthracycline regime (48, 154-157).

The addition of paclitaxel or docetaxel either in combination with an anthracycline or as a separate regimen administered before or after anthracycline based chemotherapy increases clinical and pathological response rates may increase DFS but as yet there is no significant evidence for an overall improvement in survival.

Dose-dense studies have produced conflicting results due to differences in patient selection, treatment duration and chemotherapy regimes (141, 284-287). At present, they cannot be recommended outside clinical trials.

So far no strategy has been found to be clearly superior to the others in patients with locally advanced breast cancer, and no standard chemotherapy regime has been defined.

Duration of neo-adjuvant therapy Duration NST

This has varied from 8 to 36 weeks between studies with the optimum duration still to be established. However, there is little evidence that longer schedules add any major extra benefit but at least 3-4 cycles would appear to be needed to ensure that a response is possible (158-159). Some physicians will however wish to use sequential taxanes after four courses of an anthracycline based treatment and continue to a maximum of four courses of these drugs dependent on ongoing response.

There being considerable variability in the speed of response regular monitoring to ensure ongoing benefit is essential.

Despite, modest data from prospective randomised trials of neoadjuvant systemic treatment (NST) due to the wide variety of chemotherapy schedules employed and the wide ranges of disease stage mixes, neoadjuvant chemotherapy is widely accepted as the treatment of choice for LABC, followed by surgery and radiotherapy (50, 90-92).

Most patients will respond to induction with neo-adjuvant chemotherapy (NAC) using an anthracycline-based regimen but only a small percentage achieve a complete pathological response. The addition of a taxane, either in combination or sequentially, before or after anthracycline chemotherapy increases clinical and pathological response rates. It may increase DFS, but as yet, there are no long term toxicity figures and no significant evidence of overall survival improvement. At this time, no individual regime can be recommended, with no one schedule superior to another.

Recommendations

Patients should be closely monitored throughout neoadjuvant chemotherapy to assess response and toxicity.

The standard of care is to use an anthracycline based schedule with or without a taxane.

Clinical assessment should be carried out before each course of treatment to identify non responders early and avoid inappropriate continuation of a non- effective schedule.

In responding patients chemotherapy should continue to a maximum clinical response once a tumour is considered operable, normally up to 6 or 8 cycles depending on the combination of drugs used.

Once a response plateau or patient tolerance of chemotherapy is reached in cases who have achieved a good pCR or cCR definitive local treatment should be instituted

In the absence of progression at least 2 cycles of chemotherapy should be given before concluding the patient is a non-responder. MRI after two cycles may help inform this decision (161-163).

Where there is minimal or no response a change to a non-cross resistance combination is recommended the duration being determined by toxicity and response but generally not more than 6 cycles

Trastuzumab

Trastuzumab has been shown to improve DFS and OS in the adjuvant treatment of operable breast cancer, (164) and has been given NICE recommendation for treatment in early breast cancer. It does not have a product licence for neoadjuvant therapy and does not currently have a NICE recommendation for this indication.

There are several ongoing studies evaluating the efficacy and tolerability of trastuzumab as neo-adjuvant therapy, with encouraging results in combination with a taxane or vinorelbine, which have shown pCR rates from 18-65% (165-174).

These studies have shown an apparent lack of acute toxicity, but long term safety and efficacy results are needed to determine final outcomes and safety (50).

One study does need attention (175) because of the reception received in the USA. HER-2 positive large operable breast cancers were randomly assigned to either four cycles of paclitaxel followed by four cycles of fluorouracil, epirubicin and cyclophosphamide, or to the same chemotherapy with concomitant weekly trastuzumab. The primary end point was the pCR rate. The trial was closed prematurely after inclusion of 42 patients (out of 164 planned) by the independent data monitoring committee because of an increase in the pCR rate favouring patients who received the combined treatment (25% versus 66.7%; $P=0.02$). This was a small trial and whilst encouraging it cannot change clinical practice until other completed confirmatory trials are completed with long term toxicity data (288). Post surgical adjuvant trastuzumab may be just as effective and carry less long term toxicity.

Summary

Because of the small number of patients with HER-2 positive LABC, it will not be possible to conduct a phase III trial of neoadjuvant trastuzumab in LABC, nor indeed therefore to provide enough evidence to results in a product licence for this indication.

Should trastuzumab be used in LABC?

Several factors need to be considered. Adjuvant trastuzumab has shown a survival benefit in

HER-2 positive early stage breast cancer patients who have completed definitive surgical treatment. The longer term safety profile is developing and cardiac problems do not appear to be increasing with time (289). This is a group of patients at high risk of relapse with a poor prognosis. It therefore seems reasonable to recommend adjuvant trastuzumab for a year in this group of patients but only after definitive local treatment.

The place of trastuzumab in the neoadjuvant treatment of LABC should remain in clinical trials assessing combinations in an attempt to achieve enhanced pCR rates.

At present neoadjuvant trastuzumab remains investigational

Surgery

The main goal of neoadjuvant chemotherapy is to render an inoperable tumour resectable. In recent years because of the higher response rates achieved with combination chemotherapy surgeons have been using BCS more frequently.

Post systemic therapy the tumour must be capable of macroscopic removal and a decision taken on whether to offer BCS or a mastectomy

In some trials of neo-adjuvant chemotherapy in women with large but potentially operable tumours neoadjuvant chemo has increased the rate of BCS (27, 40, 62, 67, 86) but not in all (87-89).

Inevitably the rate of BCS is higher in patients who achieve a cCR or partial CR and a poorer response may result in higher local recurrence rates (50, 176-178).

A prognostic index has been developed for in-breast recurrence and locoregional recurrence based on nodal involvement, residual pathological size, lympho-vascular involvement and a multifocal pattern of residual disease (179). This can be applied to determine a recommendation for mastectomy but is not in routine use and needs further validation.

Sentinel node biopsy is widely accepted for patients with T1-2N0M0 disease but there is no significant data in patients treated with neoadjuvant chemotherapy. The NSABP has evaluated it in one of its studies and found it to be comparable to SLN pre systemic treatment but further long term studies are needed to determine axillary recurrences in this high risk group of patients (180).

In T3 clinically node negative cases some authors have advocated SNLB prior to neoadjuvant therapy. If the biopsy is negative axillary node dissection is not performed at the time of surgery but the axilla is irradiated instead. If positive an axillary clearance is performed and the axilla only irradiated if there is a post surgical indication. At this time this is an experimental approach (92, 18).

Sentinel node biopsy should not be used for inflammatory breast cancer. (182).

The majority of patients respond to neo-adjuvant chemotherapy and the pathology specimen reveals less tumour than at the time of diagnosis. However, there is no consistent pattern of response, some tumours shrink centripetally others leave more diffuse microscopic disease. The information informing a surgical decision is therefore limited and there is concern that the conservative approach in patients will result in higher rates of local recurrence (14, 183-184).

Two studies have questioned the necessity of mastectomy (185-186) but mastectomy is still the surgery of choice and physicians must be wary of extrapolating studies with much better case mixes and large but marginally operable cancers to more extensive cases of LABC.

Surgery should only be used if a macroscopic resection can be achieved if they remain inoperable loco-region radiotherapy should be employed with salvage surgery only considered if there is a good partial response and no evidence of distant disease.

Post-operative chemotherapy

There is no clear indication for this. Nevertheless, in the US if 8 courses of chemotherapy had been given pre-operatively, no further chemotherapy is recommended (92). This was based on anthracycline/taxane sequential drug chemotherapy and was not therefore applicable to other chemotherapy approaches.

Similarly, despite the lack of an evidence base, if only 4 courses had been given preoperatively then 4 further cycles postoperatively were recommended (92).

These cases will require an individual approach and evidently there will be no studies that will be able to address and answer this question precisely.

A reasonable view would be that given the improved survival from the EBCTCG metanalysis (187) for adjuvant chemotherapy then this high risk group of patients should receive at least an equivalent amount of systemic chemotherapy as a standard postoperative programme would recommend. However, if a patient reaches a plateau response after 4 cycles and subsequent surgical histology demonstrates significant residual disease then some oncologists would feel that there had been only moderate systemic treatment and advocate a non-cross resistant chemotherapy approach often incorporating a taxane based approach. It has to be recognised that there are no definitive data to support this strategy.

Endocrine therapy post Surgery

Endocrine therapy should be started after chemotherapy and surgery following national guidelines for treatment.

Hormone Therapy

Neoadjuvant hormone therapy for ER and/or PgR positive locally advanced breast cancer is effective and may be used as an alternative to chemotherapy in post menopausal women but is associated with a lower pCR (188). There is no correlation between response to neo adjuvant hormone therapy and DFS or OS.

Neoadjuvant hormone therapy is best reserved for elderly patients with other comorbidities or who are unwilling to accept surgery or chemotherapy.

Tamoxifen has been used for many years in patients with locally advanced disease especially in elderly or unfit patients with response rates of between 33% to 68%. This wide variation is explained by a number of early studies patients not selecting patients on the basis of ER or PR positivity (188-194).

It has a low pCR rate of 1%-8% (50, 188). Responses are slow and it may be 3-6 months before the tumour is classified as unresponsive (18, 92).

Randomized studies of tamoxifen alone vs surgery (with or without adjuvant tamoxifen) in elderly patients with operable carcinoma of the breast have not shown any overall survival difference but higher local recurrence rates in the tamoxifen alone arms (194-196).

This suggests that if inoperable tumours are rendered operable by neo-adjuvant endocrine treatment then surgery should be performed if the patient is medically fit enough.

In indirect and direct comparisons aromatase inhibitors are associated with higher local responses and breast conservation procedures than Tamoxifen. There are no large trials demonstrating that breast conservation after neo-adjuvant hormone therapy is as good as mastectomy in achieving local control. However for women where mastectomy poses a significant risk hormone therapy should be considered to allow downstaging and permit less extensive surgery.

Aromatase inhibitors

Aromatase inhibitors are increasingly being used for neoadjuvant hormone therapy. They can produce response rates in ER + cases in a range from 37% to 50-70% (197-204).

Letrozole

This is the only aromatase inhibitor with a product licence for the neoadjuvant treatment of breast cancer. It produces the most potent suppression of circulating oestradiol (205) and is superior to tamoxifen as first line therapy in metastatic disease (206).

It is superior to tamoxifen in the neoadjuvant setting with response rates of 55% v 36% $p < 0.001$ after 4 months preoperative treatment with an improvement in the breast conserving surgery rate (45% letrozole v 35% tamoxifen $p = 0.02$) (207).

Anastrozole

A combined analysis of two studies comparing anastrozole with tamoxifen in advanced disease showed superiority in TTP in ER + and/or PR + tumours 10.7 v 6.4 months $p = 0.02$ (208).

It is effective as a neo-adjuvant (209-210) but the direct comparisons with Tamoxifen have been disappointing:

- The IMPACT trial comparing anastrozole, against tamoxifen against the combination of the two showed response rates of 37%, 36% and 39% respectively. Breast conserving surgery was possible in 44% for anastrozole, 31% for tamoxifen and 24% for the combination $p = 0.23$ (197).
- The PROACT study compared Anastrozole with Tamoxifen directly and showed similar response rates 39.5% v 35.4% although there was an increase in breast conserving surgery 43% v 31% $P = 0.04$ (211).

There is no indication to use anastrozole at this time outside clinical trials and it has no licensed indication for use as a neoadjuvant therapy.

Exemestane

Exemestane has been shown to be active as a neo-adjuvant treatment (212-213).

A direct comparison with tamoxifen showed an increased clinical response rate 76% v 41% $p = 0.05$ and breast conserving rate 36.8% v 20% $p = 0.05$ (199).

At present exemestane has no product license for therapy as a neoadjuvant and there are no reported trials of a head to head comparison with letrozole.

Exemestane should only be used in clinical trials as a neoadjuvant.

Novel anti-oestrogens

Faslodex is a “pure anti-oestrogen” which downregulates the oestrogen receptor is restricted to post menopausal women. It has been shown to be effective as a neo-adjuvant treatment (214).

There is no current indication for this drug as a neoadjuvant but it might be considered in rare cases as a palliative therapy in patients unable to take oral medication or in whom compliance might deny them some symptomatic benefit from hormonal manipulation.

Hormone Summary

Neoadjuvant hormone therapy is restricted to ER+ and/or PR + tumours

Steroid receptor status should be established before starting treatment to include ER/PR negative tumours but also because ER and PgR can be down regulated with treatment (215).

The optimum time to surgery is unknown with individual tumours responding at different rates. Response should be assessed at the end of three months unless there is clear tumour progression.

If the tumour is responding or stable when assessed at three months treatment should continue for at least 6 months to achieve maximum response. If the tumour is progressing and the tumour is operable then surgery should be considered. If the tumour is inoperable or the patient unwilling or to unwell for surgery second line hormones or local radiotherapy should be considered (92).

If a patient has responded to neoadjuvant hormone therapy they should continue with it post surgery despite the lack of definitive or randomized data in this patient group (50).

Hormonal agents alone should not be recommended in patients with a life expectancy exceeding two years but it remains a practical option for patients unsuitable for definitive surgery. Treatment has to be flexible to meet individual needs.

On the basis of the published data, primary treatment with letrozole in postmenopausal ER and/or PR positive women is the treatment of choice for neoadjuvant hormonal therapy. The use of ovarian suppression with aromatase inhibitors is currently investigational.

There is no information on the use of neoadjuvant hormone therapy in premenopausal women but in the unusual circumstance of a young woman not being well enough for neoadjuvant chemotherapy then ovarian suppression by oophorectomy or luteinizing hormone-releasing agonists would be appropriate

Radiotherapy

The role of radiotherapy in LABC is difficult to define. Historically, the indications for radiotherapy and the field arrangements required have depended on the proven histology at surgery which is clearly much more accurate than the pre-neoadjuvant clinical and radiological assessments. In addition to this, there is a very small evidence base informing us about the patterns of failure after neoadjuvant chemotherapy.

The recommendations for routine practice therefore have to be extrapolated to some extent from the findings from early breast cancer trials of radiotherapy. Nevertheless, it is important to understand that neoadjuvant treatment can downsize tumours in up to 90% of cases and that tumours do not necessarily shrink centripetally.

The EBCTCG overview of post operative radiotherapy in early breast cancer (216-217) showed a clear benefit for post mastectomy RT for loco-regional control leading to long-term overall survival benefit. It is counter balanced by an excess of non breast cancer deaths thought to be due to

cardiac toxicity probably caused by irradiation of the IMC lymph nodes and the significant cardiac volume included in the tangential field in older trials (218).

However, the Danish Breast Cancer Co-operative Group in their studies found no difference in ischaemic heart disease or cardiac mortality at 12 years between irradiated and non-irradiated patients. They attributed this to their radiotherapy technique that reduced cardiac dose. (219).

Given the high risk of local recurrence in LABC these findings are reassuring and help support the recommendation for radiotherapy.

The key factors associated with local occurrence are the size of the primary, pectoral fascia involvement and the number of involved nodes (220-221).

The commonest sites for local recurrence post mastectomy are the chest wall supra/ infra-clavicular regions. Recurrence in the axilla following an adequate axillary dissection is uncommon. (220-225).

More than 50% of local recurrences occur within the chest wall, with the mastectomy scar and skin being at greatest risk (220-222).

Radiotherapy after neo-adjuvant chemotherapy followed by mastectomy

There is a very modest literature for the patterns of failure in patients treated with post chemotherapy mastectomy.

In a retrospective series of patients treated by chemotherapy, modified radical mastectomy and no radiation, the final pathological extent was found to affect the risk of recurrence independently. Tumours larger than 5cm, T4 primary disease and extensively involved nodes at diagnosis increased the risk of local recurrence. In addition to this in a subset of patients achieving a pCR there was still a 20% local recurrence rate (226).

In a retrospective comparison in 579 patients receiving post mastectomy radiotherapy when there was a clear imbalance because of poor risk patients getting radiotherapy local recurrence was still reduced from 22% to 8% at 10 years $P = 0.001$ (227).

In early breast cancer, there is debate about the overall benefit of chest wall radiotherapy in intermediate risk cases (T1 N1 M0, T2 N0 M0, T2N0 with grade III and/or lymphovascular invasion) (228).

However, the EBCTCG suggests that there is a survival benefit with locoregional radiotherapy in an unplanned subset analysis showing an improved 15 year survival benefit in the one to three node positive group (216).

In patients with LABC downstaged with neoadjuvant chemotherapy, histology does not reflect the extent of the disease at diagnosis. Given the data from the overview it would seem reasonable to routinely irradiate this group of patients after downstaging recognising that these patients initially had more advanced disease.

Post mastectomy radiotherapy is the established standard of care for women with:

- Four or more pathologically involved axillary nodes (N2)
- Tumours larger than 5cm (T3) (229).

Extra nodal soft tissue extension of lymph node (ECE) metastases is seen to be an indication for post-mastectomy RT of the chest wall and axilla. Women with ECE have higher local recurrence

rates and also higher numbers of involved axillary nodes (231), and this group would be candidates for radiotherapy post NST.

Radiotherapy Recommendations

Based on very limited data it seems reasonable to recommend post mastectomy chest wall radiotherapy to:

- All patients with clinical T3 or stage III disease regardless of response to chemotherapy
- Patients presenting with clinical T3N0 disease whatever their final histology.
- Patients with positive nodes at surgery
- Patients with extracapsular extension of lymph node metastases (231).

Whether this results in an overall survival benefit in this group of patients remains to be determined.

Radiotherapy after neoadjuvant chemotherapy and breast conserving surgery

Preoperative chemotherapy can increase rates of breast conserving surgery in patients with larger primaries (81) that would not have been optimal for breast conservation at diagnosis. Surgery is aimed at the post-chemotherapy determined volume but there is a risk of higher local recurrence (81).

The MD Anderson evaluated 340 patients with BCS post neo-adjuvant chemotherapy. In patients with no post-surgery residual malignant calcifications, no residual T4 skin abnormality, negative surgical margins and no multicentric disease the 5 and 10 year recurrence rates were 5% and 10% respectively.

Factors associated with increased risk of recurrence were N2 or N3 disease, lympho-vascular space invasion in the primary core biopsy, multifocal disease and residual disease > 2cm. If T3 and T4 tumours responded leaving a "break-up" pattern the breast cancer recurrence rate was 20%.

A prognostic index using these four factors has been used to decide on the risk of local recurrence and the need for mastectomy (179).

Whilst these series show that very carefully selected cases may be offered BCS it does not directly correspond to LABC and the results need to be treated with caution

There is a clear indication for post-operative radiotherapy in all these cases in order to reduce the risk of local recurrence

Regional lymph node radiotherapy

The role of radiotherapy in irradiating the regional lymph nodes in new patients without neoadjuvant systemic treatment is not fully defined. Three trials (232-234) showed a survival benefit but two other studies have not confirmed this (235-236).

In other studies in histologically negative or 1-3 positive axillary lymph nodes there was no survival advantage to regional lymph node irradiation (235-236). Again the difficulty of extrapolating these results to LABC is evident.

After a level IIB axillary dissection 20-40% of local recurrences occurs in the supraclavicular and/or infraclavicular region (220-225, 237) with a ten year risk of axillary failure in 2-4% (220-222).

Less extensive axillary dissection is associated with a higher risk of axillary failure (232, 233).

The axillary failure rate depends on the extent of the axillary surgery and is only 2-4% in modern series (220-222).

Radiotherapy recommendations

Recommend radiotherapy of the axillary apex/supraclavicular region for patients undergoing a level I/II node dissection if four or more nodes are positive.

Radiotherapy to the full axilla should be considered in patients with inadequate axillary dissection or where it was omitted (60, 220-222, 231-233, 238).

Supraclavicular nodal failures are more common in unirradiated patients with four or more positive axillary nodes (239) and is an indication for radiotherapy.

Radiotherapy dose schedules

Radiotherapy fractionation has been addressed in the Royal College of Radiologists. Radiotherapy Dose-Fractionation Document (2006) UK recommended schedules are:

- 50 G in 25 daily fractions over 3 weeks (Grade B)
- 40 G in 15 daily fractions over 3 weeks (Grade B)
- 42.5 G in 16 daily fractions over 3.5 weeks (Grade B) (240-244)

If locoregional disease remains uncontrolled after systemic chemotherapy patients should be treated with radical radiotherapy including the whole breast, axilla and supraclavicular fossa in the absence of overt metastases. Individual cases with secondaries but persistent local symptoms may still be suitable for radical palliation in this way.

The supraclavicular field should be irradiated in all patients with 4 or more positive axillary nodes.

The American Society of Clinical Oncology recommend that after adequate surgery by a complete or level I/II axillary dissection, routine adjuvant axillary radiotherapy is not necessary and may add morbidity (245).

There is no evidence that IMC irradiation be routinely performed in any patient group.

Other Radiotherapy Approaches

Concurrent chemotherapy and radiotherapy has been used in preliminary studies (246) but should only be used in clinical trials (247).

Accelerated RT has been used in LABC (247-250) with good local control but definitive studies are needed.

Other treatments

A number of other approaches are being investigated and detailed below are a number that are more developed but which are not yet part of established practice (251).

Platinum

There appears to be synergy between platinum compounds, taxanes and herceptin and they are being investigated in the neo adjuvant setting but their role remains investigational (252, 253).

Liposomal Anthracycline

Liposomal doxorubicin formulations (liposomal doxorubicin-99) and pegylated liposomal doxorubicin show similar efficacies and favourable toxicities to conventional doxorubicin in metastatic disease and in a few small studies as neo-adjuvant in locally advanced breast cancer (254). This approach is investigational.

Gemcitabine

Gemcitabine has been shown to be active in advanced breast cancer with response rates of up to 42% in phase II trials (255) but further trials need to be done to establish its effectiveness in neo-adjuvant treatment (256, 257).

Navelbine

Navelbine has shown activity as a neoadjuvant therapy in combination treatments with epirubicin 70% – 90% (258, 259) and pCR 9% – 22% (260, 261) and to achieve a pCR of 20% in combination with Trastuzumab (262) and in combination with dose-dense Taxotere and Trastuzumab weekly a pCR of 45% in the breast and 39% in the breast and nodes (263).

The TOPIC trial of navelbine and epirubicin versus navelbine and mitozanthrone versus adriamycin and cyclophosphamide gave response rates of NE 86% NM 73% and AC 65% but the NM arm gave more neutropaenia. Neoadjuvant navelbine alone or in combination is not considered standard practice at this point and remains investigational (79).

High dose therapy

High dose chemotherapy with haematopoietic support does achieve higher objective and pathological responses but no significant improvement in DFS or OS (126, 191-198).

Dose intensive therapy and bone marrow transplantation have not been shown to have any impact on survival in inflammatory breast cancer. (261-271).

No advantage has been demonstrated for high-dose chemotherapy requiring haematopoietic stem cell support in LABC (251). This approach is reserved for clinical trials and has nothing to recommend it in routine treatment.

Bevacuzimab

Preliminary studies of Bevacuzimab in combination with a variety of agents including trastuzumab and dose dense studies are ongoing and have reported some activity but this drug can only be considered investigational in this setting (272-278).

Lapatinib

This has been shown to have activity as a monotherapy in patients with relapsed/refractory inflammatory breast cancer with a 70% ORR (290). Further trials are in progress.

Gefitinib

This has been shown to have activity on its own (50% ORR) and in combination with anastrozole (54% ORR) (291). Further trials are in progress.

Bisphosphonates

There is no evidence for the use of bisphosphonates in locally LABC.

Summary

The role of neo-adjuvant chemotherapy in locally advanced breast cancer is firmly established as the standard of care. It is now being applied to larger operable tumours in the hope of increasing the rate of BCS. The response to NST is a predictor of long term outcome with pCR strongly associated with improved DFS and OS.

The evidence base for the type and duration of chemotherapy is limited and only broad generalisations can be made from the data.

Definitive local surgery still plays a significant part in long term local control. Longer term follow up of BCS is needed to be certain that this does not result in significantly inferior local control or survival.

The role of radiotherapy in improving local control, and now survival, is becoming clearer and with more sophisticated radiotherapy techniques, the long term non-cancer death rates should be seen to reduce and improve results further.

The biological therapies offer potential hope for the future but still remain investigational.

For the future, better predictive tests for chemotherapy response will enable treatment to be individually targeted but the limitations of the efficacy data available from this relatively small area of breast cancer practice will continue to make the definition of clear treatment guidelines difficult.

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