Review of:
TA61: Capecitabine and tegafur uracil for metastatic colorectal cancer
TA176: Cetuximab for the first line treatment of metastatic colorectal cancer

This guidance was issued in:
May 2003 (TA61)
August 2009 (TA176)

The review date for this guidance is:
August 2012 (TA176)
TA 61 is currently on the list of static guidance and therefore does not have a specified review date.

Recommendation

- TAs 61 and 176 should be incorporated and cross-referenced in the on-going clinical guideline respectively. That we consult on the proposal.

Consideration of options for recommendation:

Options	Yes / No	Comment
A review of the guidance should be planned into the appraisal work programme.	No	TA61: There have been licence extensions in metastatic colorectal cancer in the UK for capecitabine (it is now licensed 1st line in combination therapy with oxaliplatin or irinotecan (with or without bevacizumab) and 2nd line in combination therapy with oxaliplatin). However, Topic Selection has confirmed that combination therapy was not considered to be an important topic, as it was already naturally filtered into clinical practice indicating that there was no clinical uncertainty. Moreover, the recommendations in TA61 do not specify monotherapy. TA176 There is new evidence from the COIN study that was ongoing at the time of TA176 which appears to indicates that cetuximab generally works less well than originally thought. However,

		TA176 did not recommend cetuximab for the overall population, therefore the COIN study results would not affect the recommendations. The COIN study has not reported on the subgroup of patients who have metastases confined to the liver, the subgroup for whom treatment is recommended in TA 176. Therefore, for both TA61 and TA176, there does not seem to be enough evidence available to merit re-appraisal at this stage.
The decision to review the guidance should be deferred	No	See above
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	No	See above
A review of the guidance should be combined with a new appraisal that has recently been referred to the Institute.	No	There are no related, newly referred topics that are planned into the work programme for the near future.
A review of the guidance should be incorporated into an on-going clinical guideline.	Yes, TA61 should be incorporated. TA176 should be cross-referenced rather than incorporated	As discussed above, there is no new evidence available for TA61 and it can therefore be incorporated into the on-going clinical guideline for the diagnosis and managaement of colorectal cancer that is due to be published in October 2011. While the same is true for TA176, the results of the further subgroup analyses of the COIN study could potentially lead to the need to update the recommendations in the future. Therefore, TA176 should not be incorporated verbatim into the on-going clinical guideline. It should instead be cross-referenced.

A review of the guidance should be updated into an on-going clinical guideline.	TBC	See above
A review of the guidance should be transferred to the 'static guidance list'.	No	The evolving evidence base around the treatment of metastatic colorectal cancer rules this option out.

Original remits

TA61: *"To advise on the clinical and cost-effectiveness of capecitabine and tegafur uracil in their licensed indications for the treatment of advanced and metastatic colorectal cancer, either as monotherapy or as combination therapy."*

TA176: *"To appraise the clinical and cost effectiveness of cetuximab within its licensed indication for the first line treatment of metastatic colorectal cancer."*

Current guidance

TA61:

1.1 Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer.

1.2 The choice of regimen (intravenous fluorouracil/folinic acid [5-FU/FA] or one of the oral therapies) should be made jointly by the individual and the clinician(s) responsible for treatment. The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual.

1.3 The use of capecitabine or tegafur with uracil to treat metastatic colorectal cancer should be supervised by oncologists who specialise in colorectal cancer.

TA176:

1.1 Cetuximab in combination with 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX), within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The manufacturer rebates 16% of the amount of cetuximab used on a per patient basis.

1.2 Cetuximab in combination with 5-FU, folinic acid and irinotecan (FOLFIRI), within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The patient is unable to tolerate or has contraindications to oxaliplatin.

1.3 Patients who meet the criteria in 1.1 and 1.2 should receive treatment with cetuximab for no more than 16 weeks. At 16 weeks,

treatment with cetuximab should stop and the patient should be assessed for resection of liver metastases.

1.4 People with metastatic colorectal cancer with metastatic disease confined to the liver who receive cetuximab should have their treatment managed only by multidisciplinary teams that involve highly specialised liver surgical services.

Relevant Institute work

Published

Improving outcomes in colorectal cancer. Cancer service guidance CSGCC. Published: June 2004. Review date: not specified.

Irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer (review of TA33). Technology Appraisal TA93. Published: August 2005. To be incorporated in the ongoing colorectal cancer Clinical Guideline.

Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Technology Appraisal TA118. Published January 2007. Review scheduled for July 2010.

Laparoscopic surgery for the treatment of colorectal cancer. Technology Appraisal TA105. Published: August 2006. Static guidance. Due to be incorporated in the ongoing colorectal cancer Clinical Guideline.

In progress

Diagnosis and management of colorectal cancer. Clinical Guideline. Expected publication date: October 2011.

Panitumumab in combination with chemotherapy within its licensed indication for the treatment of metastatic colorectal cancer. Technology Appraisal. Expected publication date: TBC.

Cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of Technology Appraisal 150 and part-review of Technology Appraisal 118)Technology Appraisal. Expected publication date: TBC.

Suspended/terminated

Irinotecan for the adjuvant treatment of colon cancer. Technology Appraisal. Expected publication date: Suspended in 2005 until further progress is made on licensing timelines.

Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy. Technology Appraisal TA150. Due: June 2008. Appraisal terminated as no evidence submission was received from the manufacturer. To be considered in an MTA along with bevacizumab and panitumumab (see above).

In topic selection

[redacted]

[redacted]

Safety information

Capecitabine: SPC updated in May 2010 with more data on adverse reactions (source: NeLM).

Recruitment to the AVANT trial of capecitabine, in combination chemotherapy with or without bevacizumab in treating patients who have undergone surgery for stage II or III colon cancer, was temporarily suspended in 2006 due to safety concerns (source: NeLM).

Cetuximab: Serious hypersensitivity reactions with panitumumab, including some fatal reactions were reported in an MHRA Drug Safety Update, May 2010. The product literature has been updated with contraindications and other recommendations.

No other relevant updates were found for the other agents used in these four appraisals.

Details of changes to the indications of the technology

Drug (manufacturer)	Details
Capecitabine (Roche)	At the time of TA61 capecitabine was licensed for first-line therapy of metastatic colorectal cancer. This has since been extended to the broader *"treatment of metastatic colorectal cancer"*, which includes use in combination both first and second lines of treatment (source: SPC). The indication considered in TA100 –

	monotherapy for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer – has also been widened to allow for use in combination with other drugs. This indication is considered in a separate proposal paper. Capecitabine is also licensed in certain circumstances for breast and gastric cancers
Tegafur uracil (Merck Serono)	No change
Oxaliplatin (Generic)	No change
Cetuximab (Roche)	No change to colorectal cancer indications. In addition to the indication covered in TA176, cetuximab is also licensed as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. This indication was to be the subject of the terminated Appraisal TA150. The use of cetuximab as a second line treatment is being investigated in the multiple technology appraisal *"cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part-review of technology appraisal 118)"* Cetuximab is licensed in specific combinations for squamous cell cancer of the head and neck.

Details of new products

Drug (manufacturer)	**Details**
Colorectal cancer vaccine (autologous tumour cell vaccine)	Phase III. UK launch planned 2012.

(Vaccinogen)	
Aflibercept (Sanofi Aventis)	Phase III as second-line combination therapy. UK launch planned Q2 2012.
MVA-5T4 (Oxford Biomedica)	Phase II as first line, combination therapy.
Nimotuzumab (YM Biosciences)	Phase II for irinotecan-refractory metastatic colorectal cancer. UK launch planned Q1 2015
Panitumumab (Takeda)	Launched as third line monotherapy, Phase III as first and second-line monotherapy (this indication is within the remit of a NICE Technology Appraisal which is currently in progress).
Perifosine (Keryx)	Phase III for advanced or metastatic colorectal cancer. UK launch not anticipated for >5 years.
Picoplatin (Poniard Pharmaceuticals)	Phase III for metastatic colorectal cancer.
Regorafenib (Bayer)	Phase III for metastatic colorectal cancer.

On-going trials & unpublished

Trial name	**Details**
TA61	
Xeloda or UFT (Tegafur-uracil) With Folinic Acid in Advanced or Metastatic Colorectal Cancer	Ongoing Estimated completion date: January 2011
Study of Bevacizumab Alone or Combined With Capecitabine and Oxaliplatin as Support Therapy in Metastatic Colorectal Cancer Patients	Bevacizumab included in both treatment arms: may not reflect UK practice Ongoing Estimated completion date: December 2010
A Study of Xeloda (Capecitabine) as a First-Line Therapy in Patients With Metastatic Colorectal Cancer	Completed in 2009

A Study of Xeloda (Capecitabine) in Patients With Metastatic Colorectal Cancer	Completed (~2008)
The MAX Study: Mitomycin C, Avastin and Xeloda in Patients With Untreated Metastatic Colorectal Cancer	Completed (~2007)
Leucovorin and Fluorouracil With or Without Oxaliplatin Compared to Capecitabine With or Without Oxaliplatin in Treating Patients With Metastatic Colorectal Cancer	Currently recruiting Estimated completion date: not stated
Oxaliplatin and Bevacizumab (Avastin™) With Either Fluorouracil and Leucovorin or Capecitabine in Treating Patients With Advanced Colorectal Cancer	Ongoing Estimated completion date: Not stated
A Study of Avastin (Bevacizumab) in Combination With XELOX or FOLFOX-4 in Patients With Metastatic Colorectal Cancer.	Completed (~2008)
A Study of Xeloda (Capecitabine) in Patients With Metastatic Colorectal Cancer	Completed (~January 2008)
TA176	
Combination Chemotherapy With or Without Cetuximab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer (COIN trial)	Estimated completion date: May 2009 Currently in follow up

Predictive Factors for the Optimization of Cetuximab in the Treatment of Patients With Advanced Colorectal Cancer	Ongoing Estimated Primary Completion Date: October 2011 Estimated Study Completion Date: December 2013

Proposal for updating the guidance

If the guidance is to be updated as an appraisal, it would be scheduled into the work programme accordingly.

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline(R) In-Process and Embase. References from November 2005 (TA61); June 2008 (TA176); May 2009 (TA212) onwards were reviewed. The results of the literature search are discussed in the 'Appraisals comment' section below.

Implementation

A submission from Implementation on TAs 100 and 176 is attached at the end of this paper. A proposal for a review of TA 100 is considered in a separate paper.

With regard to TA176, the use of cetuximab has been increasing since TA176 was published. However, as cetuximab has been licensed for the treatment of various types of cancer, it is not possible to distinguish to what extent this is due to the TA176 recommendations.

No submission was received from Implementation on TAs 61 or 212.

Equality and diversity issues

TA 61 – There were no specific equality issues addressed in the guidance although individual preferences for intravenous or oral treatment was considered.

TA176 – No equality issues were identified and specifically addressed in the Guidance.

Appraisals comment:

TA61 – colorectal cancer (first line) (metastatic) – capecitabine and tegafur uracil

We recommend that TA61 is incorporated in the on-going clinical guideline. In TA61, guidance was issued on the then marketing authorisation for first line monotherapy with capecitabine only. Capecitabine is now licensed 1st line in combination therapy with oxaliplatin or irinotecan, with or without bevacizumab, and 2nd line in combination therapy with oxaliplatin. However, Topic Selection has confirmed that combination therapy was not considered to be an important topic, as it was already naturally filtered into clinical practice indicating that there was no clinical uncertainty. Moreover, the recommendations in TA61 do not specify capecitabine monotherapy. Tegafur has had no changes to its licence.

TA176 – colorectal cancer (first line) (metastatic) – cetuximab

The Committee noted the following ongoing clinical trial related to this appraisal: NCT00182715 is a phase III randomised controlled trial evaluating first-line use of cetuximab for metastatic colorectal cancer (COIN trial). It aims to determine whether the addition of cetuximab to continuous oxaliplatin plus fluoropyrimidine chemotherapy improves overall survival when compared with either continuous or intermittent oxaliplatin plus fluoropyrimidine chemotherapy.

Since the publication of this guidance there has been no change to the marketing authorisation of cetuximab with regard to colorectal cancer, and no new interventions or comparators have come to market since the original guidance was issued. However, the first results from the COIN trial have become available and indicate negative results for cetuximab. Previous trials have shown that cetuximab is effective only in those patients whose tumours have a normal form of a gene called KRAS. The COIN trial results demonstrated that adding cetuximab to the standard chemotherapy did not improve survival in these patients. However, there was a suggestion that patients who received capecitabine/oxaliplatin with cetuximab showed no benefit, whereas those who received fluourouracil/oxaliplatin with cetuximab did show a trend to benefit. Further analyses of the COIN data were planned to explore the reasons for these differences. Results also indicated that patients who received the intermittent approach spent 10 weeks less on chemotherapy than patients in the control arm and experienced fewer side-effects. However, patient survival was 1.4 months shorter with intermittent chemotherapy. Further analyses of this comparison and patients quality of life experience on these two approaches to treatment are planned.

The manufacturer of cetuximab has highlighted that the patient population eligible for recruitment to the COIN study differs fundamentally to those eligible for treatment in NICE guidance TA 176 since patients recruited into the COIN trial were not required to have metastastic disease confined to the liver. The manufacturer's economic model submitted for TA 176 focussed on a subgroup of people who have metastatic disease confined to the liver that is unresectable. As NICE did not recommend cetuximab for the overall

population, it would appear that the COIN study results would not affect the recommendations.

Consequently, there does not seem to be sufficient evidence available to merit a re-appraisal of TA176. However, given the potential of further subgroup analyses from the COIN study it should not be incorporated verbatim in the on-going clinical guideline. Instead, it is recommended that TA176 is cross-referenced in the on-going guideline.

Key issues

For TA61, there have been licence extensions for capecitabine in its use in metastatic colorectal cancer in that it is now licensed 1st line in combination therapy with oxaliplatin or irinotecan (with or without bevacizumab) and 2nd line in combination therapy with oxaliplatin. However, Topic Selection has confirmed that combination therapy was not considered to be an important topic, as it was already naturally filtered into clinical practice indicating that there was no clinical uncertainty. Moreover, the recommendations in TA61 do not specify monotherapy. TA61 should not be appraised at this stage and can therefore be incorporated into the guideline.

For TA176, there is new evidence from the COIN study that was ongoing at the time of TA176 which appears to indicates that cetuximab generally works less well than originally thought, with possibly some difference between different combinations of cetuxumab with chemotherapy. However, TA176 did not recommend cetuximab for the overall population, but only for the subgroup of patients who have metastases confined to the liver. The COIN study has not reported on this subgroup, so it would not affect the positive recommendation in TA176. However, the potential differences between different combination therapies in the overall population may need appraising at some later stage when the results of the further analyses are available. Therefore TA176 should not be re-appraised at this stage and cross-referenced in the guideline.

GE paper sign off: Elisabeth George 24 03 11

Contributors to this paper:

Information Specialist: Tom Hudson
Technical Leads: Raisa Sidhu/Jennifer Priaulx
Technical Adviser: Zoe Charles
Implementation Analyst: Mariam Bibi
Project Manager: Kate Moore

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION PROGRAMME

Guidance Executive Review

Technology appraisal TA: 100/176: Colorectal cancer (first line, adjuvant) - capecitabine, tegafur uracil, oxaliplatin, cetuximab

1. Routine healthcare activity - IMS HEALTH Hospital Pharmacy Audit Index (HPAI)

This section provides information on prescribing cost and volume for drugs issued in hospitals in England. The data are obtained from the IMS HEALTH Hospital Pharmacy Audit Index. All costs stated in this report are based on estimated cost.

1.1 IMS HEALTH Hospital Pharmacy Audit Index (HPAI) – capecitabine

Figure 1 Trend in the cost of prescribing capecitabine in hospitals in England

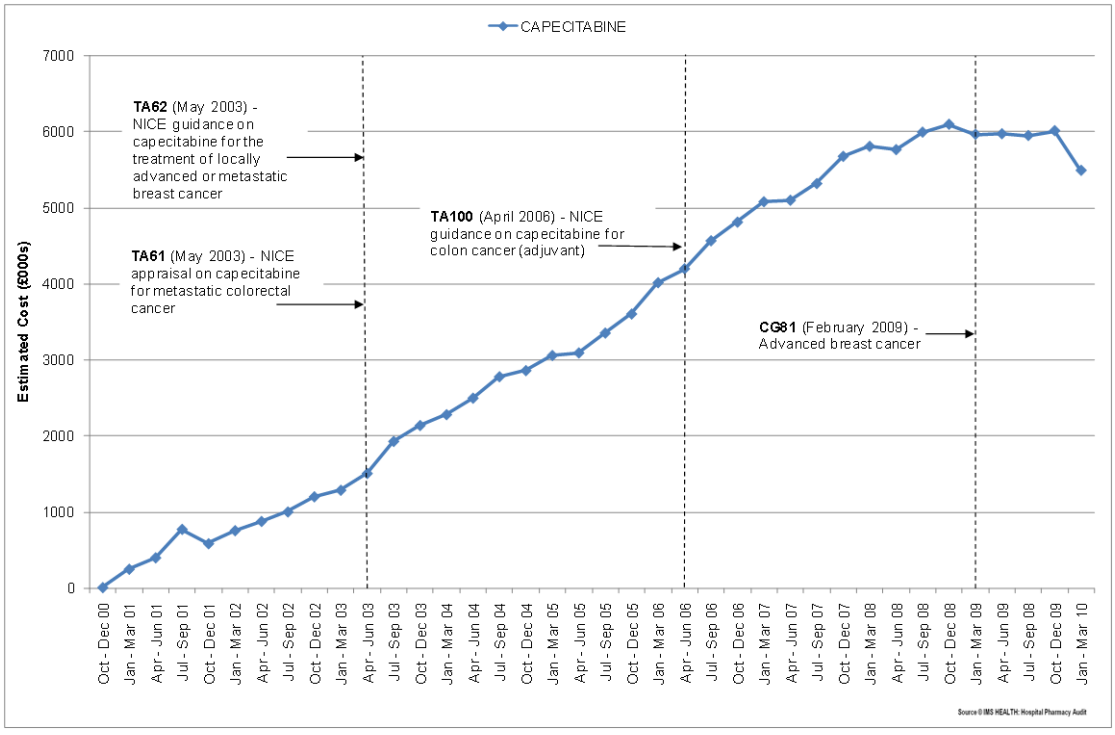
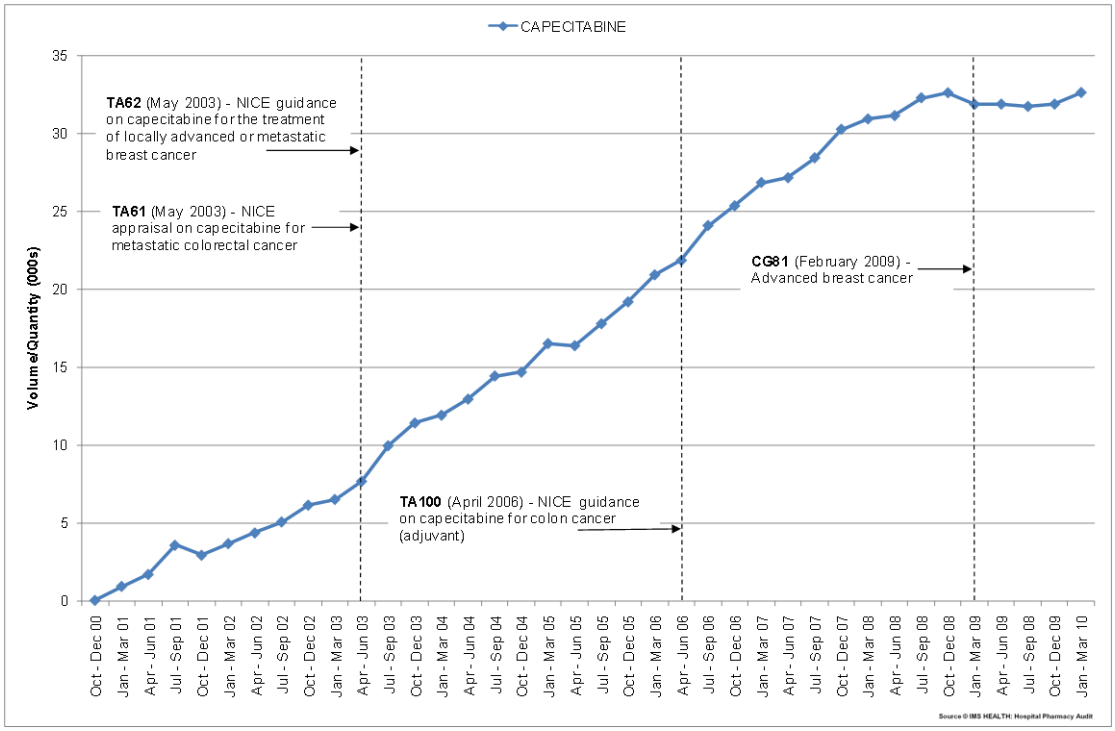


Figure 2 Trend in the volume of prescribing capecitabine in hospitals in England



The above charts show that following the publication of NICE technology appraisal 100 (and other related appraisals), the prescribing costs and volume for capecitabine continued to increase. In the quarter January to March 2006, prior to the publication of NICE technology appraisal 100, the costs were £4,011,083. By January to March 2009 the estimated costs had reached £5,962,059. In the quarter January to March 2010, the estimated costs dropped to £5,488,679. However prescribing volume did not follow the same pattern and has remained around 31,000 items since the first quarter of 2009. This fall in costs during the final quarter of 2009/10 could be for a number of reasons but the continuing level of prescriptions at the same time suggests a change in prescribing behaviour to using smaller pack sizes or dosages. It is unclear yet whether this is a temporary or ongoing trend.

This data must be interpreted with caution and cannot necessarily be attributed to increases in prescribing for colon cancer as data do not link to diagnosis.

1.2 IMS HEALTH Hospital Pharmacy Audit Index (HPAI) – oxaliplatin

Figure 3 Trend in the cost of prescribing oxaliplatin in hospitals in England

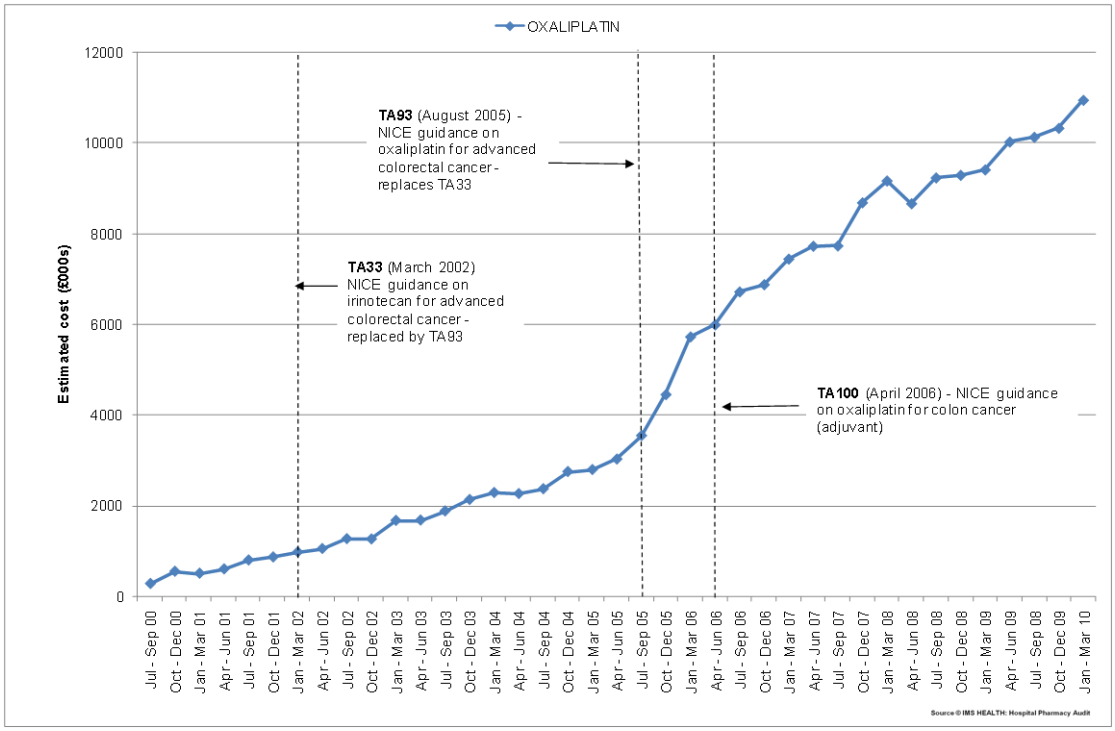
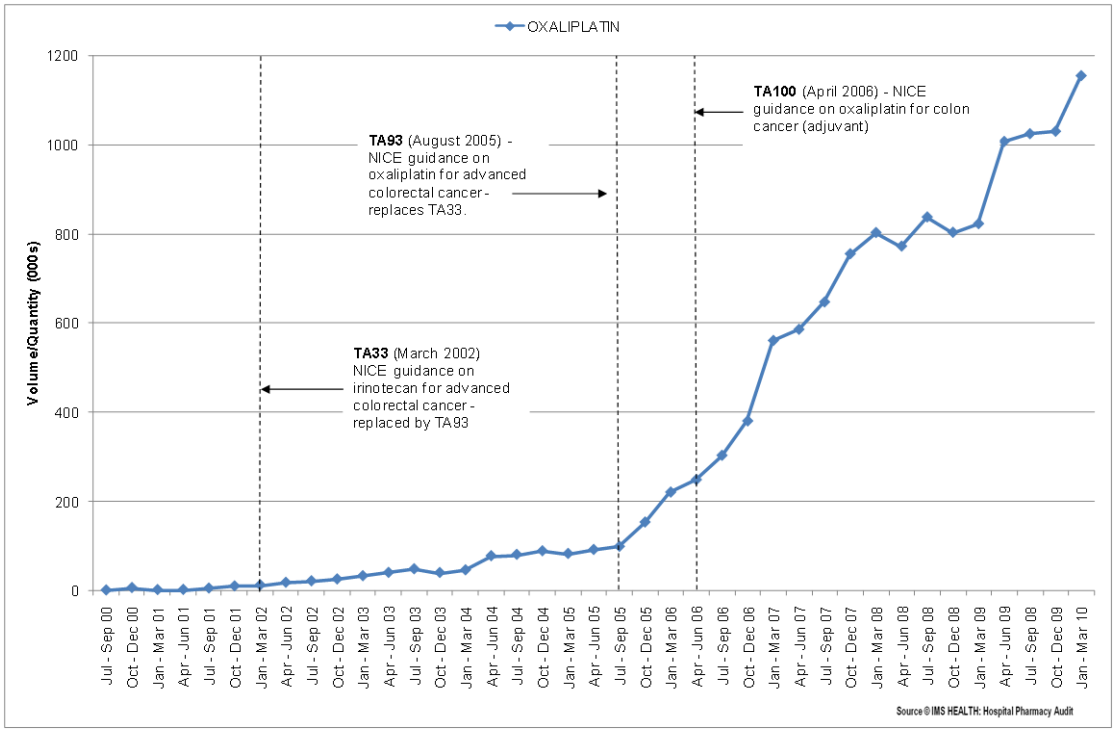


Figure 4 Trend in the volume of prescribing oxaliplatin in hospitals in England

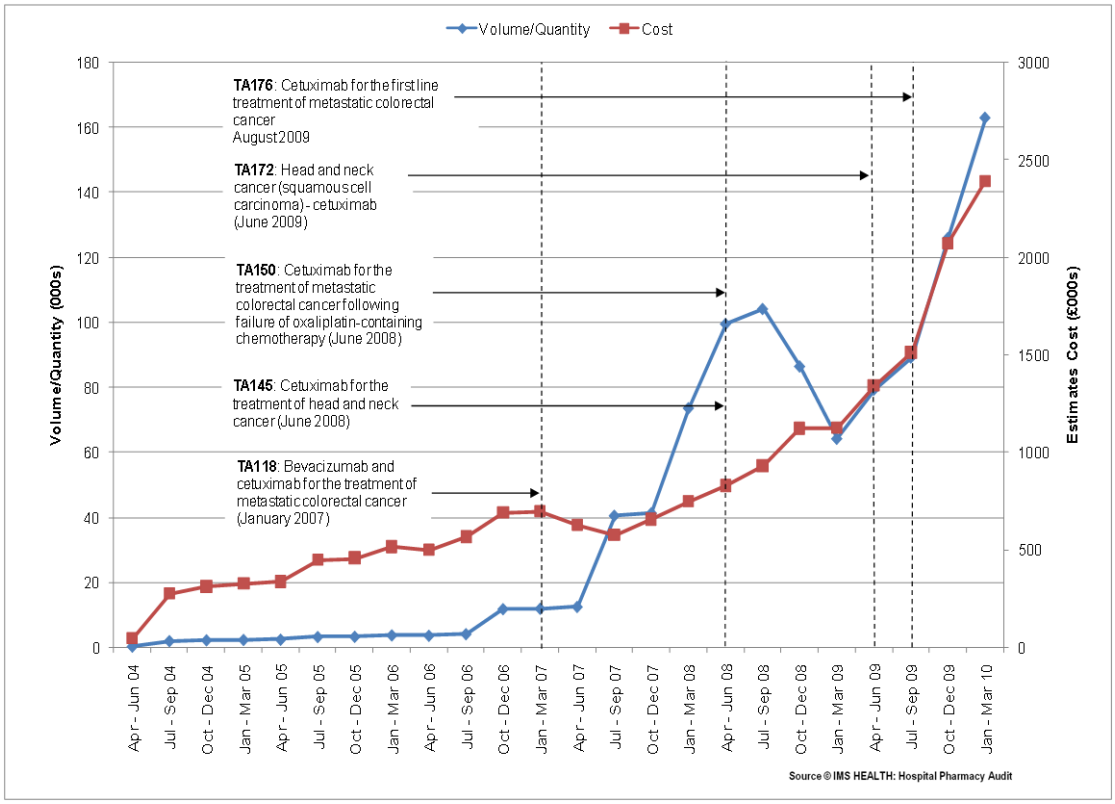


The above charts show that following the publication of NICE technology appraisal 100 (and other related appraisals) the prescribing costs and volume for oxaliplatin continued to increase. In the quarter January to March 2006 prior to the publication of NICE guidance, the costs were £5,723,986. By January to March 2010 the estimated costs had reached £10,951,995. The slight discrepancies between the trends on the graphs for cost and volume may be related to the availability and use of different vial sizes and generic versions.

This data must be interpreted with caution and cannot necessarily be attributed to increases in prescribing for colon cancer as data do not link to diagnosis.

1.2 IMS HEALTH Hospital Pharmacy Audit Index (HPAI) – cetuximab

Figure 5 Trend in the cost and volume of prescribing cetuximab in hospitals in England



The above chart shows that the costs of prescribing cetuximab have increased consistently over the period to March 2010. The volume/quantity has however fluctuated. This may potentially be in response the outcomes of NICE appraisal decisions. It is not possible to be certain why the trends in volume/quantity and costs do not mirror each other but this may be due to trends in the availability and use of different sized vials.

Notes:

- The IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI) collects information from pharmacies in hospital trusts in the UK. The IMS HPAI database is based on 'issues' of medicines recorded on hospital pharmacy systems. 'Issues' refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.
- Volume/Quantity: This is the number of packs of a medicine that are issued. They should not be added together due to differences in dosages/pack sizes.
- Cost (in £s): Estimated costs are calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost. Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.
- Ideally data would show the total number of patients prescribed a medicine and the volume and duration of treatment. However, the current datasets do not facilitate this type of analysis. Cost and volume therefore need to be considered together to provide the closest approximation. Cost provides a more accurate view of the total amount of a medicine dispensed. However, it does not provide an indication of the number of patients prescribed a medicine. Volume therefore provides an indication of the number of packs used, although it does not account for patients receiving different dosages or durations.
- Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance.

2.1 Department of Health (2009) Uptake of NICE approved cancer drugs 2007/2008 London: Department of Health

An analysis of prescribing data across cancer networks. Data show a 73% increase in prescribing of capecitabine from 2005 to 2007/08 and a 28% reduction in variation across networks; a 179% increase in prescribing of oxaliplatin from 2005 to 2007/08 and a 23% reduction in variation across networks (NB data is not linked to diagnosis).

Tegafur/uracil was excluded from this study as low usage prevents meaningful comparisons of median usage and variation.