NICE National Institute for Health and Care Excellence

NICE guidance

Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer

Technology appraisal guidance
Published: 27 May 2003

www.nice.org.uk/guidance/ta61

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Oral therapy with capecitabine 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 capecitabine) 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 to treat metastatic colorectal cancer should be supervised by oncologists who specialise in colorectal cancer.

2 Clinical need and practice

2.1 Colorectal cancer is one of the most common malignancies in the UK, with an annual incidence of about 47 cases per 100,000 individuals. In 1999, 31,000 new cases of colorectal cancer were reported in England and Wales, and in 1998 almost 15,000 deaths were reported.

2.2 Colorectal cancer is rare in people under the age of 40 years. Approximately 41% of individuals with colorectal cancer are aged over 75 years, and 52% of deaths from colorectal cancer occur in this age group.

2.3 Colorectal cancer is defined as advanced if, at presentation or recurrence, it is either metastatic or so locally invasive that surgical resection is unlikely to be carried out with curative intent. Approximately 30% of individuals diagnosed with colorectal cancer present with advanced disease. Approximately 50% of those individuals who do not have advanced disease at presentation will subsequently develop this condition. Individuals with advanced colorectal cancer may experience a wide range of physical and psychological symptoms resulting in decreased quality of life. The 5-year survival rate is, on average, less than 5%.

2.4 The management of advanced colorectal cancer is mainly palliative, and involves a combination of specialist treatments (palliative surgery, chemotherapy and radiation), symptom control and psychosocial support. The aim is to improve both the duration and quality of the individual's remaining life, while also controlling symptoms. Early chemotherapy before onset of symptoms has been shown to prolong survival and improve overall quality of life.

2.5 Individuals with advanced disease who are sufficiently fit (those with a World Health Organization [WHO] performance status of 2 or better) are usually treated with systemic chemotherapy as first- or second-line therapy. In individuals with a WHO performance status of 3 or 4 the adverse effects of chemotherapy may often be judged to outweigh the potential benefits, although the decision depends on the individual's clinical circumstances.

2.6 The standard chemotherapy regimen is typically a combination of 5-fluorouracil (5-FU) and folinic acid (calcium folinate, leucovorin). Thymidylate synthase (TS),

a key enzyme in pyrimidine biosynthesis, is inhibited by 5-FU, and folinic acid (FA) enhances TS inhibition by increasing the intracellular folate pool, thus stabilising the 5-FU–TS complex. However, an increasing number of alternative chemotherapeutic options are under evaluation.

2.7 There are different 5-FU regimens, in which the drug is given either by intravenous infusion or bolus injection. There is considerable variability in current UK practice because of a lack of consensus over the optimum regimen. Although the rates obtained in individual trials have shown variation, there is some evidence to suggest that infusional regimens, for example the Lockich and de Gramont, may be more effective in terms of progression-free survival, tumour response, safety, toxicity and quality of life than bolus regimens, for example the Mayo. However, infusional regimens are more complex to administer and the use of central venous lines increases the rate of complications, such as infection and thrombosis.

2.8 Approximately 60% of individuals experience a response or a period of stable disease following first-line 5-FU/FA therapy. There is evidence from 5 RCTs that early chemotherapy for advanced disease improves survival by 3 to 6 months compared with a policy of deferring chemotherapy until required for symptom relief. In the 5 studies, median survival was increased from a range of 5 to 9 months to a range of 7.5 to 14 months. However, the benefits of therapy must be considered against the side effects of treatment, the potential need for multiple hospital visits and, in many cases, the problems and anxieties of having a central venous line.

3 The technology

3.1 Capecitabine

3.1.1 Capecitabine (Xeloda) is a fluoropyrimidine carbamate precursor of 5-FU. It is given orally and is converted via several enzymatic steps to give intratumoural release of 5-FU. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase, is found at higher levels in tumour tissues than in normal tissue, thereby reducing systemic exposure to 5-FU.

3.1.2 Capecitabine is indicated for first-line monotherapy of metastatic colorectal cancer. The recommended dose of capecitabine is 1,250 mg/m^2 twice daily for 14 days, followed by a 7-day rest period before another cycle of treatment.

3.1.3 The listed costs of 60 150-mg tablets and 120 500-mg tablets of capecitabine are £44 and £295 respectively (excluding VAT; BNF 44, September 2002). Based on an assumed body surface area of 1.7 m^2, the acquisition cost (excluding VAT) of treating an individual with capecitabine for 105 days (5 cycles) is £1,463. Costs may vary in different settings because of negotiated procurement discounts.

3.2 Tegafur with uracil

3.2.1 Tegafur is a 5-FU prodrug, meaning that after administration it is metabolised into the pharmacologically active compound 5-FU. Tegafur is given in combination with uracil, which inhibits the degradation of 5-FU, resulting in sustained higher levels of 5-FU in tumour cells. FA is usually added to the tegafur and uracil (UFT) combination to act as a modulator. These drugs can be taken orally.

3.2.2 UFT (Uftoral) is indicated for first-line treatment of metastatic colorectal cancer in combination with FA. Each capsule contains tegafur 100 mg plus uracil 224 mg.

3.2.3 The recommended dose of UFT is tegafur 300 mg/m^2 (with uracil 672 mg/m^2) daily, combined with oral FA 90 mg/day, given in 3 divided doses (preferably

every 8 hours) for 28 days. Subsequent courses are repeated at 7-day intervals, giving a treatment cycle of 35 days.

3.2.4 The list cost of 21 UFT tablets is £67 (Monthly Index of Medical Specialties, February 2003). Based on an assumed body surface area of 1.7 m^2, the acquisition cost (excluding VAT) of treating an individual with UFT for 105 days (3 cycles) is £1,358. FA obtained at a cost of £3.78 per 15-mg tablet incurs an additional cost of up to £1,905. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The appraisal committee considered evidence from a number of sources (see section 8).

4.1 Clinical effectiveness

Capecitabine

4.1.1 Two phase 3 randomised controlled trials (RCTs), recruiting 602 and 605 individuals, and 1 pooled analysis of these study data were reviewed. Both RCTs compared capecitabine with a bolus (Mayo) 5-FU/FA regimen and were identical in design. Both studies included individuals with untreated, locally advanced or metastatic colorectal cancer, most of whom had undergone previous surgery. Although neither RCT was undertaken under blinded conditions because of the different routes of administration (oral or intravenous), both studies used an independent committee to review outcomes. The primary outcome measure in both trials was tumour response rate. Both studies were adequately powered to demonstrate equivalence in overall response rates.

4.1.2 Differences in median overall survival were not statistically different at the 5% significance level in either RCT, with values of 12.5 and 13.3 months for capecitabine and 5-FU/FA respectively in 1 study, and 13.2 and 12.1 months respectively in the other study. The pooled study also did not report any statistically significant difference in overall survival.

4.1.3 In both studies, the overall response rate was statistically significantly higher in the capecitabine groups than in the 5-FU/FA groups when outcomes were assessed by study investigators ($p=0.005$ and $p=0.013$). However, when the independent review committee assessed outcomes, these response rates were statistically significantly higher in only 1 of the studies ($p=0.0001$). When the data from both studies were pooled, response rates statistically favoured capecitabine irrespective of who carried out the assessment ($p<0.0002$ for the investigator assessment and $p<0.0001$ for the independent review committee assessment).

4.1.4 Neither study reported a statistically significant difference in mean duration of

response between the capecitabine and 5-FU/FA groups, nor was a difference reported for the pooled data. Neither study, nor the pooled analysis, reported any statistically significant differences in time to disease progression, death or treatment failure between the capecitabine and 5-FU/FA groups.

4.1.5 Neither of the studies reported any statistically significant difference in global quality of life as measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

4.1.6 With regard to treatment-related adverse events, the pooled analysis of the 2 trials indicated that individuals in the capecitabine groups reported less diarrhoea (48% versus 58%, p<0.001), stomatitis (24% versus 62%, p<0.001), nausea (38% versus 47%, p<0.001) and alopecia (6% versus 21%, p<0.001) of all grades than those in the 5-FU/FA groups. Patients in the capecitabine groups also had less grade III/IV neutropenia (2% versus 21%, no p-value available) and grade III stomatitis (2% versus 15%, p<0.0001), and less frequent hospitalisation for adverse events (12% versus 18%, p=0.002), but reported more hand–foot syndrome (54% versus 6.0%, no p-value available) and grade III hyperbilirubinaemia (18% versus 3%, p<0.0001). In the pooled analysis, treatment mortality was 1% for each group.

Tegafur with uracil (UFT)

4.1.7 Two large, open, phase 3 RCTs (Studies 011 and 012) were reviewed. These trials recruited 816 and 380 individuals respectively. No independent review committee was used to compensate for the fact that the assessors were aware of treatment allocation. Study 011 compared UFT/FA with 5-FU/FA administered using the Mayo regimen, whereas Study 012 compared UFT/FA with 5-FU/FA administered using a modification of the Mayo regimen, where treatment was repeated every 35 days instead of the standard 28 days. This non-standard variation of the Mayo regimen is a less dose-intensive regimen and has not been tested for efficacy. In Study 011, individuals recruited in the USA received UFT plus FA 75 mg/day, while those in non-USA centres received UFT plus FA 90 mg/day. Study 011 used overall survival as the primary endpoint and was powered to demonstrate equivalence of the 2 treatments as non-inferiority of survival. Study 012 used time to disease progression as the primary endpoint, and was powered to detect

a hazard ratio (HR) of 1.4 between the groups. A third study of crossover design was also identified, which assessed patient preference for UFT/FA compared with intravenous 5-FU/FA.

4.1.8 In Study 011, median survival time was 12.4 months in the UFT/FA group and 13.4 months in the 5-FU/FA group. The HR for 5-FU/FA over UFT/FA was 0.96 (95% confidence interval [CI] 0.83 to 1.13). In Study 012, median survival time was 12.2 months in the UFT/FA group and 10.3 months in the 5-FU/FA group. The HR for 5-FU/FA over UFT/FA in this study was 1.14 (95% CI 0.92 to 1.42). A secondary analysis showed that individuals from the USA sites in Study 011, who received lower-dose FA, had worse overall survival than the total study population.

4.1.9 In Study 011 the median time to disease progression was statistically significantly greater in the 5-FU/FA group than in the UFT/FA group (3.8 months versus 3.5 months, p=0.01), although the actual difference was 10 days. No statistically significant difference in time to disease progression was reported in Study 012.

4.1.10 In both studies there were no statistically significant differences between treatment arms with regard to overall tumour response rates. The rates in the UFT/FA and 5-FU/FA groups were 11.7% and 14.5% respectively in Study 011, and 10.5% and 9.0% respectively in Study 012. No statistically significant differences in duration of response were reported (actual values were not reported).

4.1.11 In Study 011, compared with 5-FU/FA, UFT/FA was associated with statistically significantly less diarrhoea (67% versus 76%, p=0.006), nausea/vomiting (67% versus 75%, p=0.02), mucositis (24% versus 75%, p<0.001), neutropenia (13% versus 77%, p<0.001) and thrombocytopenia (21% versus 31%, p<0.001) of all toxicity severity grades. UFT/FA was also associated with less grade III/IV mucositis (1% versus 20%, p<0.001), neutropenia (1% versus 56%, p<0.001), thrombocytopenia (0% versus 2%, p=0.003) and anaemia (3% versus 7%, p=0.03). Increased bilirubin, without other liver function abnormalities, was statistically significantly more common in individuals treated with UFT/FA than in those treated with 5-FU/FA (39% versus 22%, p<0.001). In Study 012, UFT/FA treatment resulted in statistically significantly fewer episodes of stomatitis/mucositis (18% versus 55%, p<0.001), neutropenia (11% versus 67%, p<0.001), thrombocytopenia (18% versus 28%, p=0.025) and anaemia (76% versus 89%, p=0.002) of any grade than 5-FU/FA treatment. UFT/FA treatment resulted in

statistically significantly less grade III/IV stomatitis/mucositis (2% versus 16%, p<0.001) and neutropenia (3% versus 31%, p<0.001). In all, 127 individuals were hospitalised during the study: 59 (31%) in the UFT/FA group and 68 (37%) in the 5-FU/FA group (p-values not reported).

4.1.12 Health-related quality of life was measured in both studies using either the Functional Living Index-Cancer or EORTC QLQ-C30; no statistically significant differences in outcomes were reported between the treatment groups in either study. An unpublished preliminary report of a phase 2 randomised study in 202 individuals indicated that scores for functional and symptom scales were either improved or unchanged in the UFT/FA group but worse in the 5-FU/FA group.

4.1.13 The only information available on preferences for treatment was a 37-patient crossover study in which individuals received either UFT (300 mg/m^2/day) plus FA (90 mg/m^2/day) for 28 days every 5 weeks, or intravenous FU (425 mg/m^2/day) plus FA (20 mg/m^2/day) for 5 days every 4 weeks. They were then crossed-over to the other treatment regimen for the second treatment cycle. Therapy preference questionnaires were completed before the first and after the second treatment cycle. Of the 31 individuals who completed the questionnaire, 84% preferred the UFT/FA regimen. The reasons for this preference included being able to take medication at home, experiencing less stomatitis and diarrhoea, and being able to use a tablet instead of having an injection.

4.2 Cost effectiveness

Capecitabine

4.2.1 Two economic evaluations of capecitabine compared with 5-FU/FA were identified, 1 conducted by the manufacturer and the other by the assessment group. Both evaluations assumed equivalent effectiveness, and thus only evaluated associated costs from an NHS perspective. Both models included costs associated with drug acquisition, chemotherapy administration (including inpatient stays) and adverse event management.

4.2.2 The manufacturer estimated the costs of capecitabine and 5-FU/FA (using the

Mayo bolus regimen) to be approximately £2,700 and £5,000, respectively. The assessment group estimated these costs to be £2,100 and £3,600, respectively. The assessment group also estimated the cost of 5-FU/FA to be £6,300 when the de Gramont infusional regimen was used and £3,500 when the modified de Gramont infusional method, which does not generally require inpatient administration, was used. In all instances, capecitabine was the least costly treatment option.

Tegafur with uracil

4.2.3 Both the manufacturer and the assessment group conducted economic analyses that compared UFT/FA with 5-FU/FA; both assessed costs from an NHS perspective and included categories of costs such as drug acquisition, chemotherapy administration (including inpatient stays), and adverse event management. A cost-minimisation study was also identified, although it was of limited use because it was from a non-UK perspective and did not specify the comparator regimen (for example Mayo or de Gramont).

4.2.4 The manufacturer's cost-effectiveness analysis compared UFT/FA with 5-FU/FA based on a Mayo regimen. The analysis used adverse events as the health outcome of interest although the evaluation was conducted separately for the 2 RCTs, and the costs of UFT/FA and 5-FU/FA were found to be £3,600 and £6,100 respectively for Study 011, and £3,200 and £4,900 respectively for Study 012.

4.2.5 The assessment group's cost-minimisation analysis showed a cost of approximately £3,500 both for UFT/FA and for 5-FU/FA, administered using either the Mayo or modified de Gramont outpatient-based regimen.

4.3 Consideration of the evidence

4.3.1 The committee reviewed the evidence available on the clinical and cost effectiveness of capecitabine and UFT, having considered evidence on the nature of the condition and the value placed by users on the benefits of capecitabine and UFT/FA by people with colorectal cancer, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective

use of NHS resources.

4.3.2 In the absence of patient preference data from adequately designed studies, the committee took particular note of the opinions of both the professional and patient representatives regarding the advantages of oral compared with intravenous administration of chemotherapy, and of the potential problems of concordance with oral treatments. The patient representatives particularly emphasised that the vast majority of individuals expressed a strong preference for oral drugs provided that effectiveness was not compromised, because they reduce the disruptive impact of chemotherapy on individuals' lives and give them greater control over the management of their disease.

4.3.3 The committee was satisfied that the phase 3 RCT data demonstrated that both capecitabine and UFT/FA were likely to have clinical effectiveness similar to that of 5-FU/FA administered by the bolus Mayo regimen. The appropriateness of using the Mayo regimen as a comparator was questioned because of evidence that suggests that infusional regimens may be more effective and less toxic. Indirect comparison of the oral drugs with infusional regimens might therefore suggest that the oral drugs are less effective. However, this evidence has not been formally appraised, and both the professional experts and the assessment group questioned its robustness. The committee did not therefore consider it sufficiently conclusive to be the basis of a recommendation against the use of the oral treatments. However, the committee also firmly believed that an appropriately designed RCT was required to carry out a direct comparison of the effectiveness of the oral treatments versus the infusional regimens. In addition, the committee considered there was insufficient evidence to enable a distinction to be made in terms of effectiveness between the 2 oral agents.

4.3.4 There are also differences in the contraindications and side-effect profiles of the individual oral and intravenous regimens, and the committee appreciated that the choice of the most appropriate treatment regimen might depend on the individual's circumstances. The committee therefore concluded that intravenous regimens may be preferable under certain circumstances, and that capecitabine and UFT/FA should thus be available as options for treatment rather than as the preferred choice.

4.3.5 The committee considered that, given the lack of compelling evidence for a

difference in effectiveness between the regimens, the correct approach to evaluation of cost effectiveness was cost minimisation. They took note of the variations in the estimates of the total costs obtained from the submitted models, and overall were convinced that the oral drugs were cost-effective compared with 5-FU/FA regimens, principally on the basis of the potential cost savings related to the method of administration. They were also aware that the reduced burden of preparation and administration on specialist staff might potentially allow reallocation of clinical resources.

5 Further research

5.1 Further research is required to determine the place of capecitabine and tegafur with uracil in the treatment of metastatic colorectal cancer. In particular, RCTs are needed to assess the use of these oral treatments compared with infusional 5-FU/FA regimens. Such studies should include evaluations of quality of life, acceptability and cost effectiveness.

6 Implications for the NHS

6.1 Given the available evidence, a conservative estimate of the cost savings that would be associated with all individuals receiving capecitabine instead of bolus 5-FU/FA is £10.5 million, including VAT. This is based on the assumption that 7,000 people receive capecitabine (costing £2,100 per person as estimated by the assessment group) instead of bolus Mayo 5-FU/FA (costing £3,600 per person as estimated by the assessment group). The savings would be similar if it is assumed that capecitabine is used in preference to the modified de Gramont regimen (costing £3,500 per person as estimated by the assessment group). However, this estimated cost saving is higher if the calculations are based on the assumption that people would otherwise receive the de Gramont infusional regimen 5-FU/FA (costing £6,250 per person as estimated by the assessment group) or on the manufacturer's cost estimates.

6.2 If it is assumed that 7,000 people receive UFT/FA (costing £3,400 per person as estimated by the assessment group) instead of 5-FU/FA administered using the Mayo or modified de Gramont outpatient-based regimen, there could be savings of up to £1.4 million. However, if 7,000 people receive UFT/FA instead of the unmodified de Gramont infusion regimen, there could be a reduction in costs of nearly £20 million.

6.3 However, it is unlikely that such savings would be realised in terms of 'cash' for 2 reasons: the estimates represent amounts of resources that would remain within the system (but might nevertheless be redeployed); and the estimates are based on average costs (for example, of days in hospital avoided), some of which are fixed costs and therefore will not be saved, but could be available for other purposes.

7 Implementation and audit

7.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

7.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

7.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has metastatic colorectal cancer and the doctor responsible for their care thinks that capecitabine and tegafur with uracil is the right treatment, it should be available for use, in line with NICE's recommendations.

7.4 Clinicians with responsibility for treating people with metastatic colorectal cancer should review their current practice and policies to take account of the guidance set out in section 1.

7.5 Local guidelines, protocols or care pathways that refer to the care of people with metastatic colorectal cancer should incorporate the guidance.

7.6 To measure compliance locally with the guidance, the following criteria can be used. Further details on suggestions for audit are presented in section 10.

7.7 For the first-line treatment of metastatic colorectal cancer, either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option.

7.8 The individual and the clinician(s) responsible for treatment decide jointly on the choice of regimen (intravenous 5-FU/FA or 1 of the oral therapies) after an informed discussion about the relative clinical and cost effectiveness, the side-

effect profile of each treatment option and the preferences of the individual.

7.9 The use of capecitabine or tegafur with uracil to treat metastatic colorectal cancer is supervised by an oncologist who specialises in colorectal cancer.

7.10 Local clinical audits on the care of people with metastatic colorectal cancer could also include measurement of compliance with accepted clinical guidelines or protocols.

8 Appraisal committee members

The appraisal committee is a standing advisory committee of NICE. Its members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. The appraisal committee meets 3 times a month except in December, when there are no meetings. The committee membership is split into 3 branches, with the chair, vice-chair and a number of other members between them attending meetings of all branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St George's Hospital, London

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice, Staffordshire

Dr Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy & Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Professor John Brazier
Health Economist, University of Sheffield

Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Mike Davies

Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Dr Cam Donaldson
PPP Foundation Professor of Health Economics, School of Population and Health Sciences & Business School, Business School – Economics, University of Newcastle upon Tyne

Professor Jack Dowie
Health Economist, London School of Hygiene & Tropical Medicine

Dr Paul Ewings
Statistician, Taunton & Somerset NHS Trust, Taunton

Ms Sally Gooch
Director of Nursing, Mid-Essex Hospital Services NHS Trust, Chelmsford

Miss Linda Hands
Clinical Reader in Surgery, University of Oxford

Ms Ruth Lesirge
Lay Representative, previously Director, Mental Health Foundation, London

Dr George Levvy
Lay Representative, Chief Executive, Motor Neurone Disease Association, Northampton

Dr Gill Morgan
Chief Executive, NHS Confederation, London

Professor Philip Routledge
Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Mr Miles Scott
Chief Executive, Harrogate Health Care NHS Trust

Professor Andrew Stevens (Vice-Chair)

Professor of Public Health, University of Birmingham

Professor Mary Watkins
Professor of Nursing, University of Plymouth

Dr Norman Waugh
Senior Lecturer & Public Health Consultant, University of Southampton

9 Sources of evidence considered by the committee

The assessment report for this appraisal was prepared by The University of Sheffield, School of Health and Related Research:

- Ward S, Kaltenthaler E, Cowan J, et al. (2002) A Review of the Evidence for the Clinical and Cost Effectiveness of Capecitabine and Tegafur with Uracil for the Treatment of Metastatic Colorectal Cancer.

The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document. Consultee organisations were provided with the opportunity to appeal against the FAD:

- Manufacturer/sponsors:
  - Bristol-Myers Squibb
  - Roche Products Limited
- Professional/specialist and patient/carer groups:
  - Association of Coloproctology of Great Britain and Ireland
  - Association of Surgeons of Great Britain and Ireland
  - Beating Bowel Cancer
  - British Geriatrics Society
  - British Psychosocial Oncology Society
  - British Oncology Pharmacy Association
  - CancerBACUP
  - Colon Cancer Concern
  - Department of Health

  - Macmillan Cancer Relief
  - National Cancer Alliance
  - Royal College of General Practitioners
  - Royal College of Nursing
  - Royal College of Physicians
  - Royal College of Radiologists
  - Royal Pharmaceutical Society of Great Britain
  - Welsh Assembly Government
  - Welsh Cancer Network
- Commentator organisations (without the right of appeal):
  - Croydon Primary Care Trust
  - MRC Clinical Trials Unit
  - National Cancer Research Institute
  - National Cancer Steering Group
  - NHS Quality Improvement Scotland.

The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the appraisal committee discussions and provided evidence to inform the appraisal committee's deliberations. They gave their expert personal view on capecitabine and tegafur with uracil for metastatic colorectal cancer by attending the initial committee discussion and/or providing written evidence to the committee. They were also invited to comment on the ACD:

- Professor David Cunningham, Consultant Medical Oncologist, Specialist in Gastrointestinal Cancer and Lymphoma, The Royal Marsden Hospital
- Dr Matthew Seymour, Senior Lecturer & Honorary Consultant, ICRF Cancer Medicine Research Centre

- Dr Chris Twelves, Beaston Oncology Centre, Western Infirmary, University of Glasgow
- Jola Gore-Booth, Chief Executive, Colon Cancer Concern
- Lynne Jones, Resources Librarian, Colon Cancer Concern.

10 Detail on criteria for audit of the use of capecitabine and tegafur with uracil for metastatic colorectal cancer

Possible objectives for an audit

An audit on the treatment of people with metastatic colorectal cancer could be carried out to ensure that capecitabine and tegafur with uracil are being used appropriately.

Possible people to be included in an audit

An audit could be carried out on people with metastatic colorectal cancer referred over a suitable time period, for example 6 months or a year.

Measures that could be used as a basis for audit

The measures that could be used in an audit of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer are as follows.

Measures that could be used as a basis for audit

Criterion	Standard	Exception	Definition of terms
For the first-line treatment of metastatic colorectal cancer an individual is given the option of oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid)	100% of people diagnosed as having metastatic colorectal cancer	None	Clinicians will have to agree locally on how the offer of the option of oral therapy as an alternative to intravenous 5-FU/FA regimens is documented for audit purposes

Criterion	Standard	Exception	Definition of terms
The individual and the clinician(s) responsible for treatment decide jointly on the choice of regimen after an informed discussion of the following: • the relative clinical and cost-effectiveness of each treatment option and • the side-effect profile of each treatment option and • the preferences of the individual	100% of people diagnosed as having metastatic colorectal cancer	None	Clinicians will have to agree locally on how the joint decision will be documented for audit purposes
An oncologist specialising in colorectal cancer supervises the use of capecitabine and tegafur with uracil	100% of the people receiving capecitabine or tegafur with uracil	None	Clinicians will have to agree locally on how supervision of the use of capecitabine and tegafur with uracil is defined and documented for audit purpose

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows:

Numerator divided by the denominator, multiplied by 100.

Numerator: Number of patients whose care is consistent with the criterion plus number of patients who meet any exception listed.

Denominator: Number of patients to whom the measure applies.

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.

Update information

Minor changes since publication

June 2018: The recommendations were updated because tegafur with uracil is no longer available.

March 2014: Implementation section updated to clarify that capecitabine and tegafur with uracil are recommended as options for treating metastatic colorectal cancer. Additional minor maintenance update also carried out.

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