A review of the evidence for the clinical and cost effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer

Rapid review protocol – Final DRAFT

A. ***This protocol is provisional and subject to change***

B. **Details of the review team**

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C. **Full title of research question**

Clinical and cost effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer.

D. **Clarification of research question and scope**

The overall aim of this review is to evaluate the clinical and cost effectiveness of capecitabine and tegafur with uracil as first-line treatments for patients with metastatic colorectal cancer, as compared with 5-FU/FA containing regimens. It will review the use of these drugs in relation to their licensed indications. Capecitabine is indicated for first line monotherapy for metastatic colorectal cancer. Tegafur with uracil is indicated for first line treatment of metastatic colorectal cancer in combination with calcium folinate.

It will not consider the use of chemotherapy in an adjuvant setting.

The review will not only focus on differences between treatments in overall survival and disease progression rate as there is a need to consider changes in quality of life associated with new drug treatment. The review will therefore aim to include any significant impacts that such treatments may have on health-related quality of life.

More specifically the review of capecitabine and tegafur with uracil for their licensed indications in metastatic colorectal cancer aims to:

1. evaluate clinical effectiveness of the two drugs in terms of disease progression rates, tumour response and time to treatment failure
2. estimate the effect on overall survival, progression free survival and quality-of-life adjusted survival
3. evaluate the adverse-effect profile and toxicity
4. estimate the incremental cost effectiveness of the drugs in comparison to conventional therapy
5. estimate the possible overall cost in England and Wales.

In undertaking to achieve the above aims the review will also consider factors such as patient preference and compliance to treatment. Issues associated with routinely used IV agents will be considered, such as complications from catheter use.

E. **Report Methods**

Search strategy

The search will aim to identify all studies relating to capecitabine and tegafur with uracil for metastatic colorectal cancer. Search strategies will include the terms capecitabine, tegafur and uracil. The following databases will be searched: Medline, Embase, Science Citation Index (SCI), Cochrane Library, NHS CRD DARE, NHS EED and HTA, OHE HEED and Pre-Medline. Searches will not be restricted by publication type or by study design as studies which do not meet the review inclusion criteria may be important in identifying further relevant papers and current research. Current research registers will also be searched and relevant professional and research organisations contacted. Citation searches of included studies will be undertaken using the SCI citation search facility, and the reference lists of included studies and relevant review articles will also be checked.

Inclusion and exclusion criteria

Inclusion criteria:

Subjects: human patients with metastatic colorectal cancer

Intervention: capecitabine as monotherapy first line treatment; tegafur with uracil in combination with calcium folinate as first line treatment

Comparators: 5-FU/FA containing regimens for metastatic colorectal cancer

Outcome measure(s):

- survival rates
- progression-free survival
- tumour response
- time to treatment failure
- health-related quality of life
- cost

Methodology:

- systematic reviews
- randomised controlled trials
- non-randomised studies
- economic evaluations.

Data extraction strategy

Data will be extracted by one researcher, and checked by a second, using a standardised data extraction form; any disagreements will be resolved by discussion.

Quality assessment strategy

Published papers will be assessed according to the accepted hierarchy of evidence, whereby meta-analyses of randomised controlled trials are taken to be the most authoritative forms of evidence, with uncontrolled observational studies the least authoritative. The quality of systematic reviews and meta-analyses will be assessed using the guidelines from the Centre for Health Evidence based upon the Users Guides to Evidence-based Medicine (JAMA 1994; 272 17: 1367-1371).The quality of randomised controlled trials will be assessed using the Jadad scale which addresses randomisation, blinding and the handling of withdrawals and dropouts (Jadad et al Controlled Clinical Trials 1996;17:1-12).

Use of data from non-randomised studies will be considered if there is insufficient evidence from good-quality randomised controlled trials. The quality of non-randomised trials will be assessed using the guidelines from the Centre for Health Evidence based upon the Users Guides to Evidence-Based Medicine (JAMA 1994; 271: 1615-1619).

The quality of economic literature will be assessed according to the "Guidelines for authors and peer reviewers of economic submissions to the BMJ" (Drummond M F, Jefferson T O, BMJ 1996;313: 275-283).

Methods of analysis/synthesis

The precise methods of any analysis and synthesis will be determined by the availability and volume of appropriate studies reported in the literature. Meta analysis will be undertaken where appropriate.

Methods for estimating quality of life, costs and cost-effectiveness

If appropriate an economic model will be developed to synthesise the available data on survival, progression-free survival and quality of life of patients treated conventionally and with capecitabine or tegafur with uracil. Cost data from published sources, if available, or derived from published or other sources of resource and cost data will be incorporated into the above model in order to allow economic, as well as clinical, implications of treatment to be assessed. Costs will include not only those associated with the administration of chemotherapy but also provision of support for complications etc. The final outcome measures used will depend on the

literature retrieved, but are likely to include:

- cost per progression-free year gained
- cost per life year gained,
- cost per quality adjusted progression-free year gained and
- cost per quality adjusted life year gained.

A sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the treatments, with the objective of identifying how secure the results of the economic analysis are, given the current evidence.

F. **Handling the company submissions**

If any economic models are included within the sponsor submissions, the review team will undertake a detailed critical appraisal analysis of the industry models. This will allow a comparison of the sponsor and the review team models. The industry dossier will also be used to identify any RCTs or cost-effectiveness studies omitted from the systematic review. Non-RCT data from the industry submissions will also be taken into account where appropriate and when no RCT data is available.

Any 'commercial in confidence' data taken from the company submission will be underlined in the HTA report (followed by an indication of the relevant company name in brackets) so that the NICE secretariat can negotiate (before and during the Institute's consultation process) with industry the subsequent inclusion of such data in the HTA monograph publication or subsequent peer-reviewed publications.

G. **Research in progress**

Current research registers will be searched. In addition, individuals known to be active in the field of colorectal cancer research will be contacted and asked for details of any relevant research in progress.

H. **Project Management**

a. **Timetable/milestones**

The draft protocol is required by 15th April 2002
The progress report is required by 19th July 2002
The draft final report is required by 23rd September 2002.

b. **Competing Interests**

None of the authors have any financial interests in the companies producing or marketing capecitabine or tegafur with uracil. However, Dr Orr has received sponsorship to attend international oncology meetings from Astra-Zeneca (ASCO, Los Angeles, 1998), Aventis (Pharma ESMO, Athens, 1998) and Sanofi-Synthelabo (Perspectives in Colorectal Cancer, Barcelona, 2000). Dr Marples was sponsored to attend the "Perspectives in Colorectal Cancer" in Dublin in 2001 by Bristol-Myers Squibb and to attend the ECCO conference in Lisbon in 2001 by Roche. Both of these were international oncology meetings.

DR M Seymour and Professor R Hawkins to make declarations.

c. **External reviewers**

The rapid review will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the rapid review encounters particularly

challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the rapid review and will understand that their role is part of external quality assurance. We will require all peer reviewers to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will return peer reviewers' signed copies to NCCHTA. Comments from external reviewers and our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

I. Appendix: Background

Epidemiology

Colorectal cancer is the second most common fatal malignancy in the UK after lung cancer. It accounts for about 1 in 10 of all new cancers in England and Wales, and almost 1 in 8 cancer deaths[1]. In 1995, 27,200 new cases were registered in England and Wales, an incidence of 54.4 per 100,000 population. Colorectal cancer is rare below 40 years of age, and 41% of patients are over 75. The incidence is rising[2].

Although many patients have potentially good survival outcomes following surgery (with adjuvant chemotherapy in some cases), over 50% will eventually develop advanced disease and distant metastasis (typically presenting within 2 years of initial diagnosis). The most frequent site of metastatic disease is the liver. Once metastatic disease is present, the outlook for the vast majority of patients is poor, with median survival of only 6-9 months from the diagnosis of metastatic disease[3]. Survival rates at 5 years after developing advanced disease are very low (<5%).

Current service provision

The only potential for long-term survival from metastatic colorectal cancer comes from resection of liver metastases in cases where there is no evidence of extra-hepatic disease and the position and size of the metastases is favourable**.** Although post-operative complications can occur, the perioperative mortality and morbidity are now very low when operations are performed by designated surgeons. There are also rare but existent survivors after resection of lung metastases.

The majority of patients with metastatic disease are treated with cytotoxic drugs, typically fluorouracil (5FU) with folinic acid (FA). In the UK, the most common form of 5FU palliative treatment is probably the 'de Gramont' or one of its variants. These regimens comprise moderately high dose folinic acid given, together with one or two bolus injections of 5FU and a high-dose 5FU infusion, over a 48 hour infusion period and repeated fortnightly. The average duration of therapy is four to six months. About 60% of patients have either a response or a period of stable disease with first-line 5FU-based therapy, but in all cases this is temporary. Second-line therapy is considered both for the "primary non-responders" and for all the people who responded when they then eventually but inevitably progress.

Until recently, there was no accepted second line treatment other than supportive care for patients who had failed to respond to, or whose disease had progressed after, a first-line 5FU-based treatment. However, since 1998, irinotecan with supportive care has become a standard second-line treatment for patients in Europe and North America.

Recently NICE[4] has issued guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. Neither irinotecan nor oxaliplatin in combination with 5-FU/FA are recommended for routine first-line therapy for advanced colorectal cancer. It is recommended that oxaliplatin be considered for first-line therapy in combination with 5FU/FA in advanced colorectal cancer in patients with metasteses that are confined solely to the liver and may become respectable following treatment. Irinotecan monotherapy is recommended in patients who have failed an established 5FU containing treatment regimen. Raltitrexed was not recommended in the NICE guidance for the treatment of advanced colorectal cancer.

These drugs are all administered intravenously which is both inconvenient and costly. The devices, such as catheters and infusion pumps, are associated with complications such as infections, thrombosis, bleeding and pneumothorax[5]. In studies of patient preference oral therapies are preferred for the administration of palliative chemotherapy[6]. Patient compliance is

another important issue when considering whether or not intravenous or oral regimens should be used.

Description of technology

Both capecitabine and tegafur with uracil are administered orally and are therefore more convenient than the intravenous 5-fluorouracil regimes in use[5]. Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which is taken orally. It is metabolised to fluorouracil and is given as monotherapy for metastatic colorectal cancer[7]. It is also used to treat metastatic breast cancer.

Tegafur is a fluoropyrimidine. It is taken orally, in combination with uracil together with calcium folinate. Tegafur is a prodrug of fluorouracil while uracil inhibits the degradation of fluorouracil. Tegafur (in combination with uracil) is used in the management of metastatic colorectal cancer[7].

References

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3. Best L, Simmonds P, Baughan C, Buchanan R, Davis C, Fentiman I, George S, Gosney M, Northover J, Williams C. Palliative chemotherapy for advanced or metastatic colorectal cancer (Cochrane Review). *The Cochrane Library* Issue 2, 2002. Oxford: Update Software.
4. National Institute for Clinical Excellence (NICE) 2002 Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. Technology Appraisal No. 33, March 2002.
5. Cunningham D & Coleman R. New options for outpatient chemotherapy-the role of oral fluoropyrimidines. *Cancer Treatment Reviews* 2001; **27**: 211-220.
6. Sharma S. Patient selection for oral chemotherapy. *Oncology* 2001 **15 (1) Supplement**: 33-35.
7. British National Formulary (BNF) No. 42, September 2001, British Medical Association and the Royal Pharmaceutical Society of Great Britain.