Complete Summary

GUIDELINE TITLE

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

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. London (UK): National Institute for Clinical Excellence (NICE); 2003 May. 25 p. (Technology appraisal; no. 61).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Metastatic colorectal cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To examine the clinical effectiveness and cost effectiveness of capecitabine and tegafur with uracil for metastatic colorectal cancer

TARGET POPULATION

Adults with metastatic colorectal cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Capecitabine
2. Tegafur with uracil (in combination with folinic acid)

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Survival rates
    - Progression-free survival
    - Tumour response
    - Time to treatment failure
    - Quality of life
    - Adverse events
    - Patient preference
    - Compliance
- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment

report for this technology appraisal was prepared by The University of Sheffield, School of Health and Related Research [ScHARR]. (See the "Companion Documents" field.)

Identification of Studies

The search strategy aimed to identify all literature relating to the clinical and cost effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer. The main searches were conducted in April and May 2002.

Fifteen electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature. A list of databases is provided in Appendix 7.1 of the Assessment Report (see the "Companion Documents" field.

In addition, the reference lists of relevant articles and sponsor submissions were hand-searched and various health services research related resources were consulted via the Internet. These included health economics and health technology assessment (HTA) organisations, guideline producing agencies, generic research and trials registers, and specialist sites. A list of these additional sources is given in Appendix 7.2 of the Assessment Report. Citation searches were conducted on key papers and authors using the Science and Social Science Citation Index facilities.

A combination of free-text and thesaurus terms were used. "Population" search terms (e.g., colorectal, colon, rectum, neoplasm, carcinoma, adenocarcinoma, etc.) were combined with "intervention" terms (e.g., Capecitabine, Xeloda, Fluoropyrimidine, tegafur, uftoral, etc.). Three searches were performed in Medline; the first was the main Medline search, the second was for the epidemiology of colorectal cancer, and the third search was performed to identify further references specifically on the two 5-Fluorouracil regimens (de Gramont and Mayo Clinic). Copies of the search strategies used in the major databases are included in Appendix 7.3 of the Assessment Report.

No language or date restrictions were applied to the searches. The search performed in Medline for the epidemiology of colorectal cancer was limited to 1990-present to ensure that only recent data were reviewed. No language or study/publication type restrictions were applied to the main searches. An economic evaluations filter was used in the main searches performed in Medline and Embase to assist with the identification of articles for the cost effectiveness aspect of the review (refer to Appendix 7.4 of the Assessment Report).

Inclusion and Exclusion Criteria

The titles and abstracts of the papers identified through the search process outlined above were assessed for relevance to the study question using the following criteria.

Inclusion Criteria

Subjects: adults with metastatic colorectal cancer

Intervention: capecitabine or tegafur with uracil plus leucovorin (UFT/LV) used alone as first-line treatment

Comparators: 5-fluorouracil plus leucovorin (5-FU/LV) regimens for metastatic colorectal cancer

Outcome measures to include the following:

- Survival rates
- Progression-free survival
- Tumour response
- Time to treatment failure
- Health-related quality of life
- Adverse events
- Patient preference
- Compliance
- Cost

Methodology, to include at least one of the following:

- Systematic reviews or meta-analyses
- Randomised controlled trials
- Non-randomised studies (for outcomes where no data from randomised controlled trials are available)
- Economic evaluations

Full copies were obtained of all those papers which appeared to be relevant, or which could not be assessed on the basis of the abstract alone.

Exclusion Criteria

Papers describing the use of chemotherapy in an adjuvant setting were excluded. Papers describing randomised phase II trials were excluded where phase III evidence was available.

NUMBER OF SOURCE DOCUMENTS

Two large phase III randomised controlled trials (RCTs) and one study of pooled data of capecitabine were identified.

Two large phase III RCTs of tegafur with uracil plus leucovorin (UFT/LV) were identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by The University of Sheffield, School of Health and Related Research [ScHARR]. (See the "Companion Documents" field.)

Quality Assessment Strategy

The randomised controlled trials were assessed for quality using the Jadad criteria. Other criteria were used to assess the quality of the meta-analyses and non-randomised studies.

Data Extraction Strategy

Data were extracted by one researcher and checked by a second using customised data extraction forms. Any disagreements were resolved by discussion.

The data extracted from the relevant studies were presented separately for the two interventions. Where available, the following data were reviewed in relation to each intervention:

- Duration of treatment
- Progression free survival
- Overall survival
- Tumour response rates
- Time to progression or death
- Duration of response
- Treatment-related deaths
- Grade 1-4 toxicities
- Quality of life
- Patient preference

No meta-analyses of the capecitabine trials were identified, although a study of pooled data was identified. No meta-analyses of the tegafur with uracil plus leucovorin (UFT/LV) trials were identified or undertaken. The two trials used different 5-fluorouracil plus leucovorin (5-FU) regimens as well as different dosages of calcium folinate (leucovorin). Meta-analysis was therefore felt to be inappropriate.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who

are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Capecitabine

Two economic evaluations of capecitabine compared with 5-fluorouracil/folinic acid (5-FU/FA) were identified, one conducted by the manufacturer and the other by the Assessment Group. Both evaluations assumed equivalent effectiveness, and thus only evaluated associated costs from a National Health Service (NHS) perspective. Both models included costs associated with drug acquisition, chemotherapy administration (including in-patient stays) and adverse event management.

Tegafur with Uracil

Both the manufacturer and the Assessment Group conducted economic analyses that compared Uftoral®/folinic acid (UFT/FA) with 5-FU/FA; both assessed costs from an National Health Service (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).

See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of oral capecitabine and tegafur with uracil for metastatic colorectal cancer

POTENTIAL HARMS

Side effects of treatment

See Tables 9 and 16 in the Assessment Report (see "Companion Documents" field) for reported toxicities of capecitabine and tegafur with uracil plus leucovorin.

CONTRAINDICATIONS

CONTRAINDICATIONS

Capecitabine (Xeloda® is contraindicated in patients with:

- A history of severe and unexpected reactions to fluoropyrimidine therapy
- Known hypersensitivity to capecitabine, fluorouracil or any of the excipients
- Known dihydropyrimidine dehydrogenase (DPD) deficiency
- Pregnancy and lactation
- Severe leucopenia, neutropenia or thrombocytopenia
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance below 30 mL/min)
- Treatment with sorivudine or its chemically related analogues, such as brivudine

Tegafur with uracil (Uftoral®) is contraindicated in patients who

- Have a known hypersensitivity to 5-fluorouracil (5-FU), tegafur, uracil or any of the excipients
- Are pregnant or attempting to become pregnant
- Are breastfeeding
- Are adolescents, children, or infants
- Have severe hepatic impairment
- Present with evidence of bone marrow suppression from previous radiotherapy or antineoplastic agents
- Have a known deficiency of hepatic CYP2A6

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- Clinicians with responsibility for treating people with metastatic colorectal cancer should review their current practice and policies to take account of the guidance (see the "Major Recommendations" field).
- Local guidelines, protocols or care pathways that refer to the care of people with metastatic colorectal cancer should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria can be used. Further details on suggestions for audit are presented in Appendix D of the original guideline document.

    - 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.
    - The individual and the clinician(s) responsible for treatment decide jointly on the choice of regimen (intravenous 5-fluorouracil/folinic acid [5-FU/FA] or one 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.
    - The use of capecitabine or tegafur with uracil to treat metastatic colorectal cancer is supervised by an oncologist who specialises in colorectal cancer.
- Local clinical audits on the care of people with metastatic colorectal cancer could also include measurement of compliance with accepted clinical guidelines or protocols.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Foreign Language Translations
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. London (UK): National Institute for Clinical Excellence (NICE); 2003 May. 25 p. (Technology appraisal; no. 61).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 May

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 May. 1 p. (Technology appraisal 61). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Review of the evidence for the clinical and cost effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer. Assessment report. NHS R & D HTA Programme. 2002 Sep 23. 146 p. Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0221. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix D of the original guideline document.

PATIENT RESOURCES

The following is available:

- The use of capecitabine and tegafur with uracil for metastatic colorectal cancer. Understanding NICE guidance - information for people with colorectal cancer and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 May. 7 p. (Technology appraisal 61).

Electronic copies: Available in English and Welsh in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N0223. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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