Complete Summary

GUIDELINE TITLE

Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2005 Aug. 39 p. (Technology appraisal; no. 93).

GUIDELINE STATUS

This is the current release of the guideline.

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SCOPE

DISEASE/CONDITION(S)

Advanced colorectal cancer (ACRC)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical effectiveness and cost effectiveness of irinotecan, oxaliplatin and raltitrexed in the management of advanced colorectal cancer (ACRC)

TARGET POPULATION

Patients with advanced colorectal cancer (ACRC)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Irinotecan in combination with 5-fluorouracil (5-FU) and folinic acid (FA) as first-line therapy or irinotecan alone in subsequent therapy
2. Oxaliplatin in combination with 5-FU and FA as first-line or subsequent therapy

Note: Guideline developers considered but did not recommend Raltitrexed (except for a clinical trial)

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Overall survival and progression-free survival
    - Health-related quality-of-life
    - Response rate
    - Adverse events
- 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Searches of Unpublished Data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 "Availability of Companion Documents" field.)

Clinical Effectiveness

Search Strategy

The search aimed to identify all literature relating to the clinical and cost effectiveness of irinotecan, oxaliplatin and raltitrexed (Appendix 3 of the Assessment Report [see "Availability of Companion Documents" field]). The main searches were conducted in June, July and August 2004. No language, study/publication, or date restrictions were applied to the main searches. Searches were performed in Medline, Excerpta Medica Database (EMBASE), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CCTR), Database of Abstracts of Reviews of Effects (DARE), Science Citation Index, Office of Health Economics–Health Economic Evaluations Database (OHE HEED), National Health Service–Economic Evaluation Database (NHS EED), NHS Health Technology Assessment Database (NHS HTA) and Cumulative Index of Nursing and Allied Health Literature (CINAHL).

Inclusion and Exclusion Criteria

Phase III randomised controlled trials were included if they compared any of the proposed indications with existing recommended indications (Section 2.3 of the Assessment Report [see "Availability of Companion Documents" field]). Primary outcomes were identified as overall survival and progression-free survival. Secondary outcomes were identified as health-related quality-of-life, response rate and adverse events. Studies were excluded if they did not report either of the primary outcomes. Use of data from phase II studies and from non-randomised studies was only considered where there was insufficient evidence from good quality phase III trials, the former being studies appropriately powered to assess efficacy outcomes, rather than those directly associated with clinical effectiveness, and both being subject to selection bias. Reports of any studies not available in English as the time scale of the review precluded time for translation.

Trials were included if they recruited participants with advanced colorectal cancer, as defined in Section 2.1.4 of the Assessment Report (see "Availability of Companion Documents" field).

Only trials which compared 5-fluorouracil (5-FU) (with or without folinic acid), irinotecan oxaliplatin or raltitrexed in licensed combinations were included in this study. Where the extent of the treatment effect was confounded by the presence of active agents from other pharmaceutical classes, the trial was excluded.

Only trials which reported at least one of the primary outcomes, overall survival (OS) and progression-free survival (PFS) were included. OS was defined as the interval from randomisation to death from any cause. PFS was defined as the interval from randomisation to first evidence of disease progression or death from any cause. Secondary outcomes, response rates, toxicities and quality of life,

were recorded where reported. Response rates were defined as the number of patients in each regimen achieving a partial or complete response, however defined. Toxicities and quality of life were abstracted as reported, however defined.

This review also includes all included studies in the original assessment report which meet the current inclusion criteria. A flow chart describing the process of identifying relevant literature can be found in Appendix 4 of the Assessment Report (see "Availability of Companion Documents" field) and a table summarizing the reasons for excluding those trials included in the previous review and the industrial submissions can be found in Appendix 5 of the Assessment Report (see "Availability of Companion Documents" field).

Cost Effectiveness

Identification of Economic Studies

Systematic literature searches were undertaken to identify all relevant studies relating to the economics of irinotecan, oxaliplatin and raltitrexed in the treatment of advanced colorectal cancer as compared with established 5-fluorouracil/folinic acid (5-FU/FA) containing regimens and best-supportive care. Details of the search strategies are reported above under "Clinical Effectiveness – Search Strategies". Hand-searching of retrieved articles and industrial submissions to NICE was also undertaken.

Inclusion/Exclusion Criteria

Studies which aimed to evaluate the cost-effectiveness of oxaliplatin, irinotecan or raltitrexed compared to established 5-FU/FA were included in the review. Economic studies were only included in the review if a full economic evaluation was reported, that is, those studies in which both the costs and benefits of chemotherapy were estimated. Partial evaluations in which either costs or benefits were estimated in isolation, and reviews of existing economic studies were excluded from the review of cost-effectiveness presented here. In addition, studies in which the methods of analysis were unclear were excluded from the review. All included studies were appraised using the checklist for assessing the quality of economic evaluations as proposed by Drummond and colleagues.

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

Seventeen phase III randomised controlled trials were found of varying methodological quality.

Economic Evaluation

Twelve studies met the inclusion criteria and were included in the review.

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

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
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 "Availability of Companion Documents" field.)

Clinical Effectiveness

Validity Assessment

Published papers were 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. Two researchers assessed papers, unblinded, for four generic dimensions of methodological quality associated with estimates of treatment effects in controlled trials. The purpose of this assessment was to give a narrative assessment of the potential for bias in the studies and, in the event that statistical synthesis (meta-analysis) was appropriate, to inform sensitivity analysis. A table summarizing data on validity assessment can be found in Appendix 6 of the Assessment Report (see "Availability of Companion Documents" field).

Data Abstraction

All abstracts were read and studies meeting inclusion criteria were identified. Data from identified studies, reviews and other evidence were extracted by two reviewers using a standardised data extraction form.

Analysis

The most complete dataset feasible was assembled. Results of eligible studies were statistically synthesised (meta-analysed) if appropriate (there was more than one trial with like populations, interventions and outcomes) and possible (there were adequate data). All analyses were by intention-to-treat. For time to event analyses (overall survival and progression-free survival), combined hazard ratios and 95% confidence intervals were calculated using the Cochrane

Collaboration Review Manager 4.2.3 software. This uses the log hazard ratio and its variance from the relevant outcome of each trial. These, in turn, were calculated using an Microsoft (MS) Excel spreadsheet authored by Matt Sydes of the Medical Research Council's (MRC's) Clinical Trials Unit, which incorporates Parmar's methods for extracting summary statistics to perform meta-analyses of the published literature for survival endpoints.

The log hazard ratio and its variance were estimated by two of Parmar's hierarchy of methods, depending on the availability of summary statistics: Method 3, which estimates the variance of the log hazard ratio indirectly from the hazard ratio and its 95% confidence intervals; and, Method 10, which estimates the log hazard ratio and its variance from survival curves. Where event numbers were not published, the 'effective number of deaths' for each arm, as calculated in the MRC spreadsheet, are reported in the Review Manager forest plots. These figures in no way affect the calculation of the hazard ratio and its variance and should be considered illustrative. Table 59, Appendix 7 of the Assessment Report (see "Availability of Companion Documents" field), records the summary statistics used for this purpose.

Note that the forest plots present hazard ratios, although they are labelled 'OR' (odds ratio) by the meta-view software.

A fixed effects model was used for the primary analyses. Heterogeneity between trial results was tested where appropriate using two tests: chi^2 and I^2 tests. The chi^2 test measures the amount of variation in a set of trials. Small p values suggest that there is more heterogeneity present than would be expected by chance. Chi^2 is not a particularly sensitive test: a cut-off of $p<0.10$ is often used to indicate significance, but lack of statistical significance does not mean there is no heterogeneity. I^2 is the proportion of variation that is due to heterogeneity rather than chance. Large values of I^2 suggest heterogeneity. I^2 values of 25%, 50%, and 75% could be interpreted as representing low, moderate, and high heterogeneity.

It was stated prospectively, that sub-group analyses would be performed on the basis of whether 5-fluorouracil (5-FU) was delivered by bolus injection or continuous infusion. This is because it is widely believed that there is a systematic difference in treatment effect based on the mode of delivery which is likely to interact in different ways with the new interventions under evaluation (see Section 2.2.1 of the Assessment Report [see "Availability of Companion Documents" field]).

Cost Effectiveness

Methods for ScHARR Economic Evaluation

The methods for the economic evaluation of irinotecan, oxaliplatin and raltitrexed in the treatment of advanced colorectal cancer are detailed in an addendum to the Assessment Report (see "Availability of Companion Documents" field).

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

The Assessment Group identified seven published economic evaluations relevant to the review (excluding the Assessment Report prepared for the original appraisal). Two manufacturers submitted economic analyses and the Assessment Group developed an economic model.

In summary, evidence from published economic evaluations, manufacturers' submissions and the Assessment Group model suggests that combination of irinotecan or oxaliplatin with 5-Fluorouracil/Folinic Acid (5-FU/FA) leads to costs per progression-free life year gained greater than £25,000. In most of the published economic evaluations, estimates of costs and benefits were accompanied by considerable uncertainty. Only the Assessment Group model calculated costs per quality adjusted life year (QALY) for combination therapies and sequences. This analysis suggests a favourable cost effectiveness estimate for irinotecan in first-line combination therapy. However, it should be noted that the FOCUS treatment costs for all study arms are underestimated, most notably for the first-line combination arms. The cost-effectiveness estimates for the GERCOR treatment sequences were favourable in comparison with the FOCUS baseline of 5-FU/FA alone followed by irinotecan, but this analysis was based on a non-randomised comparison of arms of two different trials.

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 (FAD).

- 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

- Irinotecan and oxaliplatin, within their licensed indications, are recommended as treatment options for people with advanced colorectal cancer as follows:
    - Irinotecan in combination with 5-fluorouracil and folinic acid as first-line therapy, or irinotecan alone in subsequent therapy
    - Oxaliplatin in combination with 5-fluorouracil and folinic acid as first-line or subsequent therapy.
- Raltitrexed is not recommended for the treatment of patients with advanced colorectal cancer. Its use for this patient group should be confined to appropriately designed clinical studies.

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 Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer

POTENTIAL HARMS

Side effects of treatment

- *Irinotecan*: It is associated with acute cholinergic symptoms, severe late-onset diarrhoea, myelosuppression and alopecia.
- *Oxaliplatin*: Neurotoxic side effects, which include cumulative sensory peripheral neuropathy, are dose limiting. Other side effects include gastrointestinal disturbances and myelosuppression.

For full details of side effects and other contraindications, see the Summary of Product Characteristics.

CONTRAINDICATIONS

CONTRAINDICATIONS

Irinotecan

Contraindications for irinotecan include chronic inflammatory bowel disease and bowel obstruction, bilirubin more than three times the upper limit of the normal range, World Health Organization (WHO) performance status more than 2, and severe bone marrow failure.

Oxaliplatin

Oxaliplatin is contraindicated in patients who have myelosuppression before starting first course, as evidenced by baseline neutrophils less than 2 x 109 per litre and/or a platelet count of less than 100 x 109 per litre, and in patients who have a peripheral neuropathy with functional impairment prior to first course.

For full details of side effects and other contraindications, see the Summary of Product Characteristics.

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

- Clinicians with responsibility for treating people with advanced 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 advanced colorectal cancer should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
    - A person with advanced colorectal cancer is offered irinotecan and oxaliplatin, within their licensed indications, as treatment options as follows:
        - Irinotecan in combination with 5-fluorouracil/folinic acid (5-FU/FA) as first-line therapy, or irinotecan alone in subsequent therapy, or

        - Oxaliplatin in combination with 5-FU/FA in first-line or subsequent therapy.
    - A person with advanced colorectal cancer is offered raltitrexed only as part of an appropriately designed clinical study.
- Local clinical audits on the management of advanced colorectal cancer could also include measurement of compliance with accepted clinical guidelines or protocols or with the measures for the treatment of colorectal cancer that are suggested in 'Guidance on cancer services. Improving outcomes in colorectal cancers' (see Section 8.4 of the original guideline document for details).

IMPLEMENTATION TOOLS

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

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2005 Aug. 39 p. (Technology appraisal; no. 93).

ADAPTATION

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

DATE RELEASED

2005 Aug

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

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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 is available:

- Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2005 Aug. 2 p. (Technology appraisal 93). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. Assessment report. The School of Health and Related Research (ScHARR), University of Sheffield. 2005 Apr 4. Electronic copies: Available from the NICE Web site.
- The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. Assessment report–economic addendum. The School of Health and Related Research (ScHARR), University of Sheffield. 2005 Apr 4. Electronic copies: Available from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0906. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. Understanding NICE guidance – information for people with advanced colorectal cancer, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2005 Aug. 7 p. (Technology appraisal 93).

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

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N0907. 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.

NGC STATUS

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Date Modified: 9/15/2008