TECHNOLOGY ASSESSMENT REPORTS FOR THE HTA PROGRAMME

The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer

A. Final version.

B. Details of review team

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C. Full title of research question

What is the clinical and cost-effectiveness of oxaliplatin in combination with 5-fluorouacil/folinic acid (5-FU/FA), and capecitabine monotherapy, for the adjuvant treatment of colon cancer as compared to established fluorouracil containing regimens?

D. Clarification of research question and scope

To assess the clinical and cost effectiveness of oxaliplatin in combination with 5-FU/FA, and capecitabine monotherapy (within their licensed indications), as adjuvant therapies in the treatment of patients with Dukes' stage C colon cancer after complete surgical resection of the primary tumour, as compared to adjuvant chemotherapy with an established fluorouracil-containing regimen.

Oxaliplatin in combination with 5-FU/FA is currently licensed for the adjuvant treatment of stage III colon cancer, whilst capecitabine is currently licensed only for first-line monotherapy of metastatic colorectal cancer, although it is expected that the licensed indications will be extended to include its use as adjuvant therapy within the timescale of this appraisal.

The review will focus on differences between the interventions and adjuvant chemotherapy with an established fluorouracil-containing regimen in terms of overall survival, disease-free survival, time to treatment failure, adverse effects of treatment and health-related quality of life. The objectives of the review are to:

1. Evaluate the relative clinical effectiveness of oxaliplatin (in combination with 5-FU/FA) and capecitabine (monotherapy) in terms of disease-free survival and overall survival
2. Estimate the relative effect of oxaliplatin (in combination with 5-FU/FA) and capecitabine (monotherapy) on health related quality of life
3. Evaluate the adverse effect profile and toxicity of oxaliplatin (in combination with 5-FU/FA) and capecitabine (monotherapy)
4. Estimate the incremental cost-effectiveness of oxaliplatin (in combination with 5-FU/FA), and capecitabine (monotherapy) in comparison with adjuvant chemotherapy with an established fluorouracil-containing regimen
5. Estimate the overall cost to the NHS in England and Wales

If evidence allows, consideration will also be given to different methods of delivering treatment such as bolus injection or continuous infusion.

Since the anticipated licensing timescale for irinotecan is not compatible with the scheduling of this appraisal, irinotecan will be considered within a subsequent appraisal.

E. Report methods

Search strategy
The search will aim to identify all studies relating to the use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer. In addition, supplemental searches to inform the cost-effectiveness model will be undertaken as required.

The following databases will be searched: Biosis, Medline, Embase, Web of Science, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, NHS CRD DARE, NHS EED and HTA, CINAHL, OHE HEED, ASCO database of meeting abstracts. Current research registers will also be searched and relevant professional and research organisations contacted.

Language and date restrictions will not be applied. Where possible, searches will not be restricted by publication or study type. However, due to the large number of potentially relevant references, searches in the major databases will be restricted by study type. This will be supplemented by searches designed to identify specific outcomes as required (e.g. adverse effects, quality of life).

Citation searches of included studies will be undertaken using the Web of Science citation search facility, and the reference lists of included studies, relevant review articles and sponsor submissions will also be checked.

Inclusion and exclusion criteria

Inclusion criteria:

Population:

- Patients with Dukes' stage C colon cancer after complete surgical resection of the primary tumour

Intervention:

- Oxaliplatin (in combination with 5-FU/FA)
- Capecitabine

Comparators:

- Adjuvant chemotherapy with an established fluorouracil-containing regimen

Outcome measures:

- Overall survival
- Relapse-free or disease-free survival
- Time to treatment failure
- Adverse effects of treatment / toxicity
- Health-related quality of life
- Cost

Study design:

- Systematic reviews
- Randomised controlled trials
- Economic evaluations

In the absence of evidence from good-quality randomised controlled trials the use of data from non-randomised studies will be considered.

Exclusion criteria:

- Reviews of primary studies will not be included in the analysis, but will be retained for discussion
- Studies that are considered methodologically unsound will be excluded from the review

Data extraction strategy

Data will be extracted by one researcher using a standardised data extraction form based on that proposed by the NHS Centre for Reviews and Dissemination[1] (see Appendix 1). Studies that give rise to uncertainty will be reviewed by a second researcher, and any disagreements will be resolved by discussion.

Quality assessment strategy
The quality of randomised controlled trials will be assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination[1] (see Appendix 2).

The quality of economic literature will be assessed according to the Drummond checklist[2] (see Appendix 3).

Methods of analysis/synthesis
Pre-specified outcomes will be tabulated and discussed in a descriptive synthesis. Where statistical synthesis is appropriate, the team will use summary statistics extracted from the published literature and the methodology described by Parmar and colleagues.[3] Where sufficient trials are available, a sensitivity analysis will be undertaken to see if the removal of poor quality trials (especially those with inadequate concealment of the allocation schedule) affects the results. Subject to the availability of evidence, a mathematical model will be developed to synthesise the available data on survival, disease-free survival and quality of life of patients receiving conventional treatments or either oxaliplatin in combination with 5-FU/FA or capecitabine. Costs will be incorporated into the mathematical model in order to estimate the cost-effectiveness and cost-utility of oxaliplatin in combination with 5-FU/FA and capecitabine in comparison to 5-FU/FA alone.

Methods for estimating qualify of life, costs and cost-effectiveness
The key economic outcomes from this review are cost per disease-free life-year gained, and cost per life year gained. If suitable quality of life data exists, the cost per quality-adjusted life-year of each intervention will be estimated. Disease-free survival is a surrogate clinical endpoint, and interpretation of cost-effectiveness results is unclear within a health services commissioning context. Overall survival is an unambiguous outcome measure; if appropriate the mathematical model will use overall survival rather than disease-free survival as the measure of clinical benefit. Sensitivity analyses will be undertaken to identify the key parameters that determine the cost-effectiveness of the treatments. If appropriate, multivariate Monte Carlo methods will be undertaken to generate information on the likelihood that each treatment is optimal.

F. Handling the company submission(s)

A systematic review of published cost-effectiveness and cost-utility studies will be undertaken. The review team will undertake a detailed critical appraisal of models reported within the company submissions. It is anticipated that an independent cost-effectiveness model will be developed and compared to manufacturers' models, subject to the availability of trial data (e.g. survival curves, resource use data) from the manufacturers. The manufacturers' dossiers will also be used to identify any randomised controlled trials or cost-effectiveness studies omitted from the systematic review.

Any 'commercial in confidence' data taken from the manufacturers' submission will be clearly marked in the HTA report by underlining.

G. Project management

a. **Timetable/milestones** - submission of:

The draft protocol by 14th Feb 2005
The progress report by 12th May 2005
The 'complete and near final' draft will be sent to external reviewers and the NICE Technical Lead by 11th July 2005
The draft final report by 8th August 2005

b. **Competing interests**

None of the ScHARR team has any competing interests, nor any financial interest in the companies who manufacture the drugs included in this review. Any reported concerns are detailed below:

Prof. Matt T Seymour is a member of the National Cancer Research Institute (NCRI) Colorectal Cancer Group and Chief Investigator or Co-Investigator of several on-going trials (including being a member of the QUASAR II trial management group), which may be affected by a change in standard NHS practice as a result of the review.

Prof. John Scholefield is the chair of the NCRI Colorectal Cancer Group (2003-2006). He is involved in the development of new trials in colorectal cancer.

Dr. Mark Saunders has not had any formal contracts with any pharmaceutical companies. His only advisory contract was with a company (Oxford BioMedica) who specialised in gene therapy (2002). He is involved in a range of trials (including being a member of the QUASAR II trial management group), which are supported or partially supported, by a variety of pharmaceutical companies including Roche and Sanofi-Aventis. All money has been paid to Christie Hospital and he has not gained personally from these trials. Dr. Saunders has declined a further invitation for a half-day meeting by Roche because of this NICE project. In 2001/2002 he advised Aventis on their strategy of appealing the NICE guidance. In 2002, he helped compile an educational CD for Sanofi on the adjuvant treatment of colorectal cancer.

c. **External review**

The Technology Assessment Report 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 TAR encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external reviewers' signed copies to NCCHTA. Comments from external reviewers and the Technical lead, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

Appendix 1: Data extraction form

Randomised controlled trials data extraction form

STUDY & DESIGN	DATA EXTRACTION	
Trial	REVIEW DETAILS	
	Author, year	
Study design	**Objective**	
	Publication type (ie full report or abstract)	
	Country of corresponding author	
	Language of publication	
	Sources of funding	
	INTERVENTIONS	
	Focus of interventions (comparisons)	
	Description	
	T1: Intervention group, dose, timings	
	T2: Control group, dose, timings	
	Intervention site (health care setting, country)	
	Duration of intervention	
	Length of follow up	
	STUDY CHARACTERISTICS	
	Method of randomisation	
	Description	
	Generation of allocation sequences	
	Allocation concealment?	
	Blinding level	

	Numbers included in the study	
	Numbers randomised	T1: T2:
	POPULATION CHARACTERISTICS	
	Target population (describe)	
	Inclusion / exclusion criteria (n)	
	Recruitment procedures used (participation rates if available)	
	Characteristics of participants at baseline	
	Age (mean yr.)	
	Gender (male/female)	
	Performance scale/status	
	Tumor stage	
	Other information	
	Were intervention and control groups comparable?	
	OUTCOMES	
	Definition of primary outcomes	
	Definition of secondary outcomes	
	Definition of tertiary outcomes	
	Definition of other outcomes	
	ANALYSIS	
	Statistical techniques used	
	Intention to treat analysis	
	Does technique adjust for confounding?	
	Power calculation (priori sample calculation)	
	Attrition rates (overall rates) i.e. Loss to follow-up	

	Was attrition adequately dealt with?	
	Number (%) followed-up from each condition	
	Compliance with study treatment	
	Adherence to study treatment	
	RESULTS	
	Quantitative (e.g. estimates of effect size); qualitative results; effect of the intervention on other mediating variables (Example outcomes: overall survival, relapse-free survival, disease free survival, response rates etc.)	
	Adverse effects / toxicity	
	Quality of life	
	Other information	
	SUMMARY	
	Authors' overall conclusions	
	Reviewers comments	

Appendix 2: Quality Assessment Scale

Randomised controlled trial quality assessment scale

Was the method used to assign participants to the treatment groups really random?
What method of assignment was used?
Was the allocation of treatment concealed?
What method was used to conceal treatment allocation?
Was the number of participants who were randomised stated?
Were details of baseline comparability presented?
Was baseline comparability achieved?
Were the eligibility criteria for study entry specified?
Were any co-interventions identified that may influence the outcomes for each group?
Were the outcome assessors blinded to the treatment allocations?
Were the individuals who administered the intervention blinded to the treatment allocation?
Were the participants who received the intervention blinded to the treatment allocation?
Was the success of the blinding procedure assessed?
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?
Were the reasons for withdrawal stated?
Was an intention-to-treat analysis included?

Y – item addressed; N – no; ? – not enough information or not clear; NA –not applicable

Appendix 3: The Drummond checklist[2] for assessing quality of economic literature

1. Was a well-defined question posed in answerable form?

1.1 Did the study examine both costs and effects of the service(s) or programme(s)?
1.2 Did the study involve a comparison of alternatives?
1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often?

2.1 Were any important alternatives omitted?
2.2 Was (Should) a *do-nothing* alternative (be) considered?

3. Was the effectiveness of the programmes or services established?

3.1 Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?
3.2 Was effectiveness established through an overview of clinical studies?
3.3 Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4. Were all the important and relevant costs and consequences for each alternative identified?

4.1 Was the range wide enough for the research question at hand?
4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
4.3 Were capital costs, as well as operating costs, included?

5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life-years)?

5.1 Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
5.2 Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. Were costs and consequences valued credibly?

6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements).
6.2 Were market values employed for changes involving resources gained or depleted?
6.3 Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?
6.4 Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility been selected)?

7. Were costs and consequences adjusted for differential timing?

7.1 Were costs and consequences which occur in the future 'discounted' to their present value?
7.2 Was any justification given for the discount rate used?

8. Was an incremental analysis of costs and consequences of alternatives performed?

8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

9. Was allowance made for uncertainty in the estimates of costs and consequences?

9.1 If data on costs or consequences were stochastic, were appropriate statistical analyses performed?

9.2 If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?

9.3 Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

10 Did the presentation and discussion of study results include all issues of concern to users?

10.1 Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?

10.2 Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?

10.3 Did the study discuss the generaliseability of the results to other settings and patient/client groups?

10.4 Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?

10.5 Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

References

[1] NHS Centre for reviews and Dissemination. *Report 4: Undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews*. York: University of York; 2001.

[2] Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes.* Oxford University Press, 2003.

[3] Parmar MKB, Torri VB, Stewart L, 1998, Statist. Med. 17, 2815-2834.