Cost-effectiveness of oxaliplatin and capecitabine in the adjuvant treatment of stage III colon cancer
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study evaluated the use of capecitabine and oxaliplatin in combination with 5-fluorouracil and folinic acid (5-FU/LV) in the treatment of Stage III colon cancer. The comparator for the two regimens was the standard chemotherapy treatment (5-FU/LV alone). However, two regimens of 5-FU/LV alone were identified in randomised controlled trials and these were treated differently.

The regimens compared were:

- oxaliplatin plus 5-FU/LV (2 weeks of 12 cycles: 800 mg/m2 bolus 5-FU, 1,200 mg/m2 infusional 5-FU, 400 mg/m2 leucovorin and 85 mg/m2 oxaliplatin per cycle) versus the de Gramont 5-FU/LV regimen (2 weeks of 12 cycles: 800 mg/m2 bolus 5-FU, 1,200 mg/m2 infusional 5-FU and 400 mg/m2 leucovorin per cycle), and
- capecitabine (3 weeks of 8 cycles: 35,000 mg/m2 capecitabine per cycle) versus the Mayo Clinic 5-FU/LV regimen (4 weeks of 6 cycles: 2,125 mg/m2 bolus 5-FU and 100 mg/m2 leucovorin per cycle).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with completely resected Stage III colon cancer.

Setting
The setting was not explicitly reported, although it was most probably secondary care. The economic evaluation was carried out in England and Wales.

Dates to which data relate
The effectiveness data were obtained from studies published between 1995 and 2005. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a review of published studies and authors' assumptions.

Modelling
A health-state transition model was developed to estimate the incremental cost-effectiveness of the chemotherapy.
regimens evaluated. The three health states considered in the model were alive without relapse, alive following relapse, and dead. Transitions between health states were derived from published survival curves using a 4-weekly cycle length. The time horizon of the model was the patient’s lifetime.

Outcomes assessed in the review
The outcomes assessed were the efficacy of the chemotherapy regimens (in terms of disease-free survival) and the time-dependent probability of relapse.

Study designs and other criteria for inclusion in the review
The inclusion criteria were not specified. However, efficacy data were mainly obtained from two multi-centre, international randomised controlled trials (Andre et al. 2004 and Scheithauer et al. 2003, see ‘Other Publications of Related Interest’ below for bibliographic details).

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Six studies were included in the review.

Methods of combining primary studies
A narrative method was used to combine the primary studies.

Investigation of differences between primary studies
Not reported.

Results of the review
The authors explained the methodology and the sources used to estimate patient survival, but the efficacy outcomes were not reported in this article.

Methods used to derive estimates of effectiveness
The authors made some assumptions when estimating some of the model parameters.

Estimates of effectiveness and key assumptions
The long-term survival of patients who did not relapse was assumed to be the same as that of an age-matched population of individuals with no history of colon cancer. Survival following relapse was assumed to be independent of time of relapse and adjuvant treatment received.
Measure of benefits used in the economic analysis
The summary measure of health benefit used was the quality-adjusted life-years (QALYs) gained. The life-years gained (LYG) were also reported but were not used to calculate a cost-effectiveness ratio. The utility values were obtained from the literature. The health benefits were discounted at a rate of 1.5%.

Direct costs
Discounting was applied at a rate of 6%. The costs included in the analysis were those associated with drug acquisition and administration, pharmacy handling and dispensing, infusor pumps, examinations and tests, as well as hospitalisation resource use for the management of treatment-related toxicities. The costs were obtained from the literature, from the NHS, and from personal communications. The unit costs and the resource quantities were not reported separately. The price year was 2004.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included.

Currency
UK pounds sterling (£).

Sensitivity analysis
One-way and probabilistic sensitivity analyses were performed to assess the robustness of the results. The variables tested in the one-way sensitivity analyses were the discount rates for costs and health outcomes, the utility scores, the costs and outcomes of treatment regimens, the period over which relapses may occur, and the time horizon of the model. Monte Carlo techniques were used in the probabilistic sensitivity analysis.

Estimated benefits used in the economic analysis
The mean discounted LYG were 9.87 with the 5-FU/LV Mayo Clinic regimen and 10.88 with capecitabine, (difference 1.02 LYG).

The mean discounted QALYs were 8.47 with the 5-FU/LV Mayo Clinic regimen and 9.45 with capecitabine, (difference 0.98 QALYs).

The mean discounted LYG were 10.80 with the 5-FU/LV de Gramont regimen and 12.15 with oxaliplatin (plus 5-FU/LV), (difference 1.36 LYG).

The mean discounted QALYs were 9.39 with the 5-FU/LV de Gramont regimen and 10.71 with oxaliplatin (plus 5-FU/LV), (difference 1.33 QALYs).

Cost results
The mean discounted cost was 13,239 with the 5-FU/LV Mayo Clinic regimen and 9,919 with capecitabine, (difference -3,320).

The mean discounted cost was 22,261 with the 5-FU/LV de Gramont regimen and 26,202 with oxaliplatin (plus 5-FU/LV), (difference 3,940).
Synthesis of costs and benefits
Incremental cost-utility ratios were used to combine the costs and health benefits.

The capecitabine regimen dominated the Mayo clinic 5-FU/LV regimen as it was estimated that it was more effective and less costly than the standard therapy.

The incremental cost per QALY gained of oxaliplatin (plus 5-FU/LV) if compared with the de Gramont 5-FU/LV regimen was 2,970.

Sensitivity analyses showed that the main estimates of cost-effectiveness were robust to changes in individual parameter values. Moreover, Monte Carlo simulations showed that the probabilities that capecitabine and oxaliplatin (in combination with 5-FU/LV) had an incremental cost-effectiveness ratio greater than 20,000 were 0.998 and 0.997, respectively.

Authors' conclusions
Both capecitabine and oxaliplatin regimens were expected to produce health gains at a cost considered acceptable to the National Health Service (NHS) in England and Wales.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was justified as it represented the standard practice in the authors' setting. Since two types of 5-FU/LV regimen were identified in the clinical trials, the authors were reluctant to use the trials to make indirect comparisons between capecitabine and oxaliplatin. You should decide if these represent widely used chemotherapy regimens in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness data is likely to be good as data on efficacy were mainly obtained from international multi-centre trials. However, the authors reported that the main limitation of their analysis was that patients enrolled within these trials were comparatively younger than the typical colon-rectal cancer population treated on the NHS. Hence, the long-term survival benefits associated with each intervention might have been overestimated within the model. Although the authors stated that a systematic review of the literature was undertaken, the sources searched to identify primary studies were not reported. Moreover, the health outcomes of the trials (in terms of disease-free survival) were not reported in this article. Nevertheless, the methods of survival analysis used to calculate life expectancy in the model were appropriately explained. In addition, sensitivity analyses included effectiveness parameters, which to some extent enhance the validity of the effectiveness estimates.

Validity of estimate of measure of benefit
QALYs were used as the measure of benefit. This enables comparisons with the results of other studies. The authors stated that the utility values were obtained from the literature but they did not report the methods used to derive them. The health benefits were appropriately discounted.

Validity of estimate of costs
It appears that all the costs relevant to the perspective adopted have been taken into account in the analysis. Discounting was appropriately applied as the time horizon of the model was longer than 2 years. The authors reported the cost sources and the price year. Sensitivity analyses of the costs were conducted.

Other issues
The authors compared their findings with those from other studies and discussed the differences found. The issue of generalisability was not explicitly addressed but extensive sensitivity analyses were performed. The authors' conclusions reflected the scope of the analysis. More details on the clinical data would have been helpful. The difference between
the Mayo Clinic and the de Gramont 5-FU/LV regimens, if any, was not explained.

**Implications of the study**
The results of this study suggest that both capecitabine and oxaliplatin regimens are expected to have an acceptable cost-effectiveness ratio to the NHS in England and Wales. However, the limitations surrounding the use of the available trials as a source of effectiveness data make it difficult to determine whether one or both of the interventions should be adopted for maximum benefit. Further trials, including trials using oxaliplatin-capecitabine combinations, might help clarify these issues. Meanwhile, decision-makers should evaluate the costs and benefits of the treatments for individual patients.

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**Bibliographic details**
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**Other publications of related interest**
Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information.

Andre T, Boni C, Moudedji-Boudiaf L, et al. Oxaliplatin, fluorouacil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-51.

Scheithauer W, Mckendrick J, Begbie S. Oral capecitabine as an alternative of i.v. 5-fluorouracil- based adjuvant for colon cancer: safety results of a randomised, phase III trial. Ann Oncol 2003;14:1735-53.

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antineoplastic Combined Chemotherapy Protocols /economics /therapeutic use; Capecitabine; Chemotherapy, Adjuvant; Colonic Neoplasms /drug therapy /economics /pathology; Cost-Benefit Analysis; Deoxycytidine /administration & dosage /analogs & derivatives; Fluorouracil /analogs & derivatives; Neoplasm Staging; Organoplatinum Compounds /administration & dosage; Randomized Controlled Trials as Topic; Survival Analysis

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