Pharmacoeconomic analysis of adjuvant oral capecitabine vs intravenous 5-FU/LV in Dukes' C colon cancer: the X-ACT trial


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 compared two adjuvant treatment options for the treatment of Duke's C colon cancer. The modules compared were:

- 24 weeks of eight cycles of oral capecitabine (Xeloda), 1,250 mg/m2 twice daily, days 1 to 14 every 21 days: and
- six cycles of rapid-infusion intravenous (i.v.) leucovorin 20 mg/m2, followed immediately by i.v. bolus 5-fluorouracil (FU) 425 mg/m2, days 1 to 5 every 28 days (Mayo Clinic regimen).

The 5-fluorouracil/leucovorin (5-FU/LV) treatment regimen represented the standard practice in the authors' setting.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised patients with resected, histologically confirmed Dukes' C colon carcinoma. No further inclusion or exclusion criteria were reported in the current study. The reader is referred to the following two papers which report further details of the methodology of the X-ACT study (Scheithauer et al. 2003, and Twelves et al. 2005, see 'Other Publications of Related Interest' below for bibliographic details).

Setting
The setting was not explicitly stated, but it appears to have been secondary care. Although the 164 centres included in the study were located worldwide, the economic study was carried out in the UK.

Dates to which data relate
All effectiveness data were derived from the X-ACT study that was carried out from November 1998 to November 2001. The results of the trial were reported in two papers published in 2003 and 2005. Resource use was based on actual data collected prospectively alongside the X-ACT trial. The cost data were derived from official sources published between 2004 and 2005. The price year was not explicitly reported.

Source of effectiveness data
The effectiveness data were derived from a single study, the X-ACT study (Scheithauer et al. 2003 and Twelves et al. 2005). The reader is referred to this trial for further details on the effectiveness data and the methods used to derive them.
**Link between effectiveness and cost data**

Data on medical resource use were collected prospectively on the same sample of patients as that used in the effectiveness study.

**Study sample**

Between November 1998 and November 2001, 1,987 patients from 164 centres worldwide were enrolled and randomly allocated to oral capecitabine (n=1,004) or 5-FU/LV (n=983). Power calculations or the sample selection method were not reported in the current study (see Scheithauer et al. 2003 and Twelves et al. 2005 for further details).

**Study design**

The analysis was based on an open-label multi-centre, multinational, randomised, phase III trial. It was reported that the patients were followed up for 3 years, but no losses to follow-up were reported in the current study (see Scheithauer et al. 2003, and Twelves et al. 2005 for relevant details).

**Analysis of effectiveness**

It was reported that the analysis was conducted on an intention to treat basis. The authors reported that the two treatment arms were well balanced, but no further details on the comparability of the two groups or any adjustments for confounding factors were reported. The primary outcomes used in the analysis were relapse-free survival, disease-free survival and overall survival. The survival analysis was conducted using Kaplan-Meier curves. Trial data were extrapolated beyond the study period for 5 years, 10 years and a lifetime horizon. The extrapolations were conducted by assuming a log-normal distribution for the relapse-free and overall survival data of the two treatment groups.

**Effectiveness results**

Capecitabine was more effective than 5-FU/LV regarding relapse-free survival, (p=0.0407). Differences in disease-free survival and overall survival were not statistically significant, (p=0.0528 and p=0.0706, respectively).

Regarding overall survival, the Kaplan-Meier projection demonstrated that 81.3% of patients in the capecitabine group survived at 36 months compared with 77.6% of patients receiving i.v. 5-FU/LV.

**Clinical conclusions**

Capecitabine was at least as effective as 5FU/LV in the adjuvant treatment of colon cancer.

**Modelling**

A health-state transition model was developed to assess the health care costs, quality-adjusted survival and overall cost-effectiveness of the two treatment options. The model comprised three health states: stable (including pre-relapse, disease-free and relapse-free), post-relapse (subdivided into relapse, remission and the 12-month period before death) and death. A lifetime horizon was adopted in the model.

**Measure of benefits used in the economic analysis**

The authors used quality-adjusted life-months (QALMs) gained as the measure of benefits in the economic analysis. Utility values of health states were derived from the published literature (Ramsey et al. 2000, see ‘Other Publications of Related Interest’ for bibliographic details) and authors’ assumptions. Main utility values assigned to health states were reported in the current study. Since the benefits were incurred during more than 2 years, they were discounted at a rate of 1.5%.

**Direct costs**
The health services used in the analysis were chemotherapy per g, visits for drug administration, hospitalisation costs, health care provider consultations, and the cost of an ambulance round trip. Visits for drug administration included physician consultations and visits for intravenous administration. Health care provider consultations included general practitioner office visits and home visits, specialist office visits, costs of day care, costs of accident and emergency, nurse or other office consultation, and nurse or other home visit. The costs and the quantities were reported separately for these categories. In addition, chemotherapy drug costs and medication related to the treatment of adverse events (e.g. antiemetics/antidiarrhoeals, dermatologicals/emollients, benzodiazapines, stomatologicals/triazoles, antibiotics/cephalosporins, cytokines/growth factors, octreotide) were also considered in the analysis. The unit costs were not reported for these costs, only the reported resource use (days of use) per 100 patients. Neither the unit costs nor the resources used were reported for post-treatment costs (i.e. monthly cost of maintenance during relapse, average cost during the relapse period, monthly maintenance cost during post-relapse, and average cost during the 12 months of life); only average costs were reported. In terms of the patients' costs, the authors also accounted for the cost of travel, assuming a 30-mile round trip (at 0.23 per mile) for outpatient and drug administration visits. The source of this cost was not referenced. Resources used were based on actual data collected prospectively alongside the X-ACT study, whereas all costs were obtained from published sources. Since the costs were incurred over a long period of time (more than 2 years), discounting was appropriately conducted (6% rate). The price year was not explicitly reported.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The analysis accounted for productivity losses due to time spent for outpatient and drug administration visits and due to hospitalisation. Time assumptions included travel time as well as waiting and encounter time. Time spent (in hours) was reported for each occasion and was multiplied by the average hourly compensation in the UK and was derived from a previously published study on the X-ACT trial. Since the costs were incurred over a long period of time (more than 2 years), discounting was appropriately conducted (6% rate). The price year was not explicitly reported.

**Currency**
UK pounds sterling (£).

**Sensitivity analysis**
The authors conducted one-way and multi-way sensitivity analyses to test the robustness of cost and QALM results to variability in the data. The model parameters tested in the one-way sensitivity analysis were:

- mean amount of capecitabine used (range: 430,137 to 414,180 mg);
- mean amount of 5-FU used (range: 19,820 to 19,147 mg);
- mean amount of LV used (range: 973 to 937 mg);
- health state utilities (+/-20%);
- cost per drug administration visit (+/- 20%);
- a common discount rate for the costs and benefits (3.5%);
- the total costs of medication for adverse events (+/- 20%); and
- QALMs, which were varied using a Weibull distribution.

In the multi-way sensitivity analysis, post-treatment costs (i.e. average monthly pre-relapse cost, average cost during the relapse period, and monthly maintenance cost during the post-relapse period) were varied simultaneously. The method
used to select the ranges used in the sensitivity analyses was not explicitly reported.

**Estimated benefits used in the economic analysis**
Only the incremental benefits of using capecitabine versus 5-FU/LV were reported. The projected survival gain of capecitabine was 0.5 QALMs in 36 months and 0.8 QALMs in 48 months. Over the patients' lifetime horizon, capecitabine resulted in an additional 9 QALMs gained compared with 5-FU/LV.

**Cost results**
The total costs per patient were reported.

The total costs were 3,557 per patient in the capecitabine group and 8,528 per patient in the 5-FU/LV group.

The use of capecitabine resulted in net cost-savings of 4,971 per patient.

**Synthesis of costs and benefits**
As capecitabine was more effective, resulting in 9 incremental QALMs and cost-savings compared with 5-FU/LV, no incremental cost-effectiveness analysis was needed.

One-way sensitivity analyses demonstrated the robustness of the results to variations in the key parameters of the model.

Multi-way sensitivity analyses demonstrated that the long-term cost-savings associated with using capecitabine were decreased when the costs of relapse and maintenance were low. However, capecitabine remained a cost-saving option in comparison with 5-FU/LV.

**Authors' conclusions**
"Cost savings and better outcomes make capecitabine a preferred adjuvant therapy for Dukes’ C colon cancer."

**CRD COMMENTARY - Selection of comparators**
The selection of the comparators was explicitly justified. Adjuvant 5-FU/LV would seem to represent standard practice in the authors' setting, while capecitabine has recently received approval from the European Medicines Agency Committee for Medicinal Products for Human Use. You should decide if these represent widely used technologies in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on an open-label, multi-centre, multinational, randomised, phase III trial, which was appropriate given the study question. The study referred to patients with histological confirmed Dukes' C colon cancer. However, it was unclear whether the study sample was representative of the study population because no details of the patients were provided. The patient groups were not shown to be comparable at analysis in the present study. In addition, it is not possible to comment on the internal validity of the study since the authors referred to a separate paper for details of the clinical study.

**Validity of estimate of measure of benefit**
The authors used health utility (QALMs) as the measure of benefit in the economic analysis. The health values were derived from the literature and authors' assumptions.

**Validity of estimate of costs**
The analysis of the costs was performed from the perspectives of the NHS and society. It appears that all the relevant categories of costs have been included in the analysis. The costs and the quantities were not reported separately for all cost categories, although resource use per patient was recorded. However, this would not enable the analysis to be easily reworked for other settings. Resource use was mainly based on actual data derived from a single study, while in some cases it was augmented by authors' assumptions or expert opinion. No justification was given for the assumptions concerning resource use and no statistical analysis of the quantities was performed. The costs were derived from published sources and were treated deterministically. However, extensive sensitivity analyses on both resource use and costs were conducted to assess the robustness of the estimates used. The costs and benefits were appropriately discounted but the price year was not explicitly reported, thus impeding any future reflation exercises.

Other issues
The authors compared their findings with those from other studies, finding them generally to be in agreement. The issue of generalisability of the results to other settings was not directly addressed. The authors do not appear to have presented their results selectively. The study enrolled patients with Dukes' C colon cancer and this was reflected in the authors' conclusions. As a limitation to their study, the authors reported the lack of direct measures of utility values for the stable (pre-relapse) health state after treatment, which forced the authors to make several assumptions about health utilities in both treatment arms.

Implications of the study
The authors made an explicit recommendation for changes in practice. Specifically, the results of their study support replacing 5-FU/LV with capecitabine in the adjuvant therapy for Dukes' C colon cancer in the UK.

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None stated.

Bibliographic details

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Other publications of related interest


MeSH
Administration, Oral; Antineoplastic Combined Chemotherapy Protocols /economics /therapeutic use; Capecitabine; Chemotherapy, Adjuvant /economics; Colonic Neoplasms /drug therapy; Cost-Benefit Analysis; Deoxycytidine /administration & dosage /analogs & derivatives /economics; Disease-Free Survival; Drug Administration Schedule; Drug Costs /statistics & numerical data; Fluorouracil /administration & dosage /economics; Great Britain; Health Care Costs; Health Resources /utilization; Humans; Injections, Intravenous; Leucovorin /administration & dosage /economics; Neoplasm Staging; Quality of Life; Remission Induction; Sensitivity and Specificity; Survival Rate; Time Factors; Treatment Outcome

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