Cost-effectiveness analysis of oxaliplatin compared with 5-fluorouracil/leucovorin in adjuvant treatment of stage III colon cancer in the US

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 chemotherapy with 5-fluorouracil plus leucovorin (5-FU/LV) against a combination of oxaliplatin and 5-FU/LV (the FOLFOX4 regimen). The FOLFOX 4 regimen was oxaliplatin 85 mg/m² on day 1, leucovorin 200 mg/m² on days 1 and 2, 5-FU bolus 400 mg/m² and 5-FU continuous infusion 600 mg/m² on days 1 and 2. The 5-FU/LV regimen was leucovorin 200 mg/m² on days 1 and 2, 5-FU bolus 400 mg/m² and 5-FU continuous infusion 600 mg/m² on days 1 and 2. Patients in both groups received 12 cycles of chemotherapy interrupted by 2-week intervals.

Type of intervention
Treatment.

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

Study population
The study population comprised a sub-group of the study population of the parent, MOSAIC clinical trial (Andre et al 2004). This comprised Stage III colon cancer patients. The patients' characteristics were reported in full in the current paper.

Setting
The interventions appear to have been provided by a secondary care provider in an outpatient and inpatient setting. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were mainly derived from a parent clinical trial (the MOSAIC trial) that was published in 2004 and a further study published in 1995. The resource use data were derived from individual patient history data collected during the MOSAIC trial. The unit cost data were obtained from official published sources and were reported for the price year 2003.

Source of effectiveness data
The clinical parameters associated with the interventions included DFS, recurrence rate, time of recurrence, OS and adverse event rates (e.g. neutropenia, neuropathy, nausea and vomiting, and diarrhoea).

Modelling
Disease-free survival (DFS) and overall survival (OS) from 0 to 48 months was estimated using the Kaplan-Meier method. DFS was then extrapolated to 5 years by adjusting a parametric model to the tail of the curve for patients alive
and free of disease at 36 months. OS beyond 48 months was calculated using a mathematical relationship between DFS and OS. The survival function after recurrence was estimated using a Weibull model, adjusted for time of recurrence. The authors reported that the models were estimated separately and were validated by verifying that the predicted OS curve lay within the 95% confidence limits of the respective Kaplan-Meier estimates (0 to 48 months).

Sources searched to identify primary studies
The baseline data were obtained from a large international, randomised Phase III trial, the MOSAIC trial (Andre et al. 2004). The authors’ assumptions about survival after 5 years were supported by a published randomised controlled trial (Moertel et al. 1995, see ‘Other Publications of Related Interest’ below for bibliographic details).

Methods used to judge relevance and validity, and for extracting data
The methods used to obtain the data were not reported since the authors’ intention was to analyse individual patient-level data from the MOSAIC trial (Andre et al. 2004) and to extrapolate the results to a lifetime horizon.

Measure of benefits used in the economic analysis
The measures of benefits used were the life-years (LYs), disease-free years (DFYs) and quality-adjusted life-years (QALYs). DFYs and LYs were estimated as areas under the DFS and OS curves, respectively. The utility values for relevant health states were derived from published sources that used the HUI-3 questionnaire. Utility values associated with adverse events were also derived from published literature, but the method employed to derive them was not reported. After the fourth year of follow-up, the utility values for disease-free survivors equalled those of the general population, and were obtained from published sources that employed the EQ-5D technique. The benefits were appropriately discounted at an annual rate of 3%.

Direct costs
The study reported the direct costs to Medicare. These were chemotherapy costs (drug administration, clinic visits, infusion pumps, pre-medication), second-line adjuvant chemotherapy costs, routine follow-up, the treatment of serious adverse events and toxicity, and the cost of recurrence (i.e. local recurrence, liver and lung metastasis, or disseminated disease) including the cost of possible surgery and first- and second-line chemotherapy. Resource use was mainly determined using a micro costing methodology. If data were not available, a weighted average was used. The unit costs were reported. The cost data were appropriately discounted at a rate of 3% and reported for the price year 2003.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
Productivity costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
The authors investigated uncertainty in the modelling assumptions by testing the following two scenarios:

the annual recurrence rate of patients free of disease at 5 years was assumed to be equal for both groups and declined from 1.5% at year 5 (instead of zero in the base-case analysis); and

using the same post-year 5 recurrence rates mentioned above, FOLFOX4 was assumed to have a prolonged
effectiveness beyond 5 years, therefore a relative risk reduction (RRR) of 24% was assigned to post-year 5 recurrence rates.

A lower cost scenario of treating recurrences was also tested. Lower costs arose from a group of assumptions that were reported in full. The upper limit of the 95% confidence interval (CI) around the survival curves after recurrence in both arms was used to assess the impact of a potential extension of life expectancy after recurrence attributable to innovative treatments for metastatic disease.

Uncertainty surrounding the cost-effectiveness results was investigated through a probabilistic sensitivity analysis using the bootstrap technique.

**Estimated benefits used in the economic analysis**
The benefits were calculated within the trial period (4 years) and extrapolated to 5 years and then to 50 years.

The incremental discounted benefits per patient were reported.

The use of the FOLFOX4 regimen compared with 5-FU/LV resulted in 1.32 additional DFYs, 0.83 additional LYs and 0.75 additional QALYs (95% CI: 0.09 to 1.41).

**Cost results**
The mean discounted costs were reported per patient.

The FOLFOX4 regimen cost $56,320, whereas the 5-FU/LV regimen cost $39,285. The cost-difference was $17,035.

**Synthesis of costs and benefits**
Mean incremental cost-effectiveness ratios (ICERs) were reported. The FOLFOX4 intervention compared with 5-FU/LV would cost $12,832 per DFY gained, $20,603 per LY gained and $22,804 per QALY gained.

The sensitivity analyses varied the ICER from $20,400 per QALY to $25,800 per QALY.

Assuming a willingness-to-pay of $50,000 to $100,000 per QALY gained, probabilistic sensitivity analysis demonstrated that the FOLFOX4 regimen has a 91 to 96% probability of being cost-effective.

**Authors’ conclusions**
“FOLFOX4 (oxaliplatin plus 5-fluorouracil/leucovorin) is likely to be cost-effective compared with 5-FU/LV (5-fluorouracil/leucovorin) in the adjuvant treatment of Stage III colon cancer.”

**CRD COMMENTARY - Selection of comparators**
The selection of the comparators was explicitly justified. Chemotherapy with 5-FU/LV seemed to represent standard treatment, while FOLFOX4 represented a recently approved treatment regimen in the authors’ setting. You should decide if these represent valid health technologies in your own setting.

**Validity of estimate of measure of effectiveness**
Individual patient-level data were obtained from a large international, randomised Phase III trial (MOSAIC trial) that directly compared the FOLFOX4 regimen with 5-FU/LV alone. The information reported in this paper on the MOSAIC study suggested that the quality of the evidence used is likely to have been reasonably good. Assumptions after 5 years were justified with reference to a published randomised controlled trial.

**Validity of estimate of measure of benefit**
The authors used LYS, DFYs and QALYS as the measures of benefit in the economic analysis. The derivation of LYSs...
and DFYs was adequately described. These outcomes enable comparison across diseases. The sources of the utility values were quoted. The benefits were appropriately discounted.

**Validity of estimate of costs**

The analysis of the costs was consistent with the perspective adopted in the study, but a more detailed breakdown of the costs would have been more informative. The price year and the source of the data were provided. Resource consumption reflected actual patterns of treatment. Cost estimates specific to US Medicare were used in the analysis, which implies that you should consider whether Medicare costs are likely to be similar to the costs in your own health care setting. As patient-level data were used, a bootstrapping analysis was performed. The costs were discounted appropriately.

**Other issues**

The authors reported that their cost-effectiveness results agreed with those from published studies. The authors acknowledged variation in the cost data between different health settings in the USA, but did not evaluate the impact of this on the economic results through a sensitivity analysis. A more detailed costing exercise would have been more informative to the decision-maker, whilst a detailed description of resource use would have enhanced the generalisability to other settings. The authors pointed out that the patient dataset contained limited data on the treatment of toxicities. Consequently, the costs of less serious toxicities were based on assumptions with reference to standard treatments. However, it is unlikely that these estimates would have affected the authors' conclusions. The results of the study do not appear to have been presented selectively and the authors' conclusions would appear to be an adequate reflection of the scope of the analysis. Although the authors made little comment on the limitations of their findings, they appear to have provided a balanced discussion.

**Implications of the study**

The authors endorsed the adoption of FOLFOX4 in the adjuvant treatment of patients with Stage III colon cancer. However, they pointed out that real-time follow-up data would provide more robust evidence to substantiate their conclusions.

**Source of funding**

Funded by a grant from Sanofi-Aventis.

**Bibliographic details**


**PubMedID**

17265519

**DOI**

10.1002/cncr.22512

**Other publications of related interest**

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Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Antineoplastic Combined Chemotherapy Protocols /economics /therapeutic use; Chemotherapy, Adjuvant /economics; Colonic Neoplasms /drug therapy /economics /surgery; Cost-Benefit Analysis; Female; Fluorouracil /administration & dosage /economics; Humans; Leucovorin /administration & dosage /economics; Male; Middle Aged; Neoplasm Recurrence, Local /mortality; Neoplasm Staging; Organoplatinum Compounds /administration & dosage /economics; Survival Analysis; United States

AccessionNumber
22007000871

Date bibliographic record published
30/11/2007

Date abstract record published
30/11/2007