An economic evaluation of oxaliplatin for the adjuvant treatment of colon cancer in the United Kingdom (UK)
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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 examined two adjuvant treatments for patients with Stage III colon cancer after surgical resection. These were 5-fluorouracil plus folinic acid (5-FU/FA) and oxaliplatin (OXA) plus 5-FU/FA.

The 5-FU/FA regimen consisted of a 2-hour infusion of 200 mg/m2 FA followed by a 400 mg/m2 bolus of 5-FU on day 1, then a 22-hour protracted infusion of 600 mg/m2 5-FU over days 1-2, every 14 days for 12 cycles.

The OXA plus 5-FU/FA regimen consisted of a 2-hour infusion of 85 mg/m2 oxaliplatin simultaneously with 200 mg/m2 FA followed by a 400 mg/m2 bolus of 5-FU on day 1, then a 22-hour protracted infusion of 600 mg/m2 5-FU over days 1-2, every 14 days for 12 cycles.

Type of intervention
Adjuvant treatment.

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

Study population
The study population comprised patients aged between 18 and 75 years who had undergone complete surgical resection of Stage III (any T, N1 or N2, M0) colon cancer, as defined by the presence of the inferior pole of the tumour above the peritoneal reflection (at least 15 cm from the anal margin).

Setting
The setting was a hospital. The economic study was carried out in the UK.

Dates to which data relate
The clinical and resource use data were derived from studies published in 2002 and 2004. The price year was 2003.

Source of effectiveness data
The clinical data used in the analysis were the rate of colon cancer recurrence, frequency of adverse events, overall survival, disease-free survival and mortality. Disease-free survival was defined as the time from trial randomisation to relapse or death, while overall survival was defined as the proportion of patients alive at a particular time point but not necessarily disease-free.

Modelling
The analysis assumed that the patients' first 4 years' survival matched the experience of the participants of the MOSAIC
trial in the first 4 years following randomisation. Survival after the 4th year was extrapolated from the MOSAIC estimates using Weibull distributions and assuming that survival in subsequent years matched the general mortality of the UK (no recurrences of colon cancer after the 4th year were assumed). Specifically, a parametric survival model was used after 4 years because the data in the MOSAIC trial were sparse beyond this point.

Sources searched to identify primary studies
Almost all of the clinical data (overall survival, disease-free survival and adverse events) were derived from the MOSAIC study, an international, multi-centre, randomised, prospective, clinical trial with 3-year follow-up that involved 2,246 patients. Mortality was derived from standard UK life tables. Some assumptions about survival were made. In particular, no recurrences of colon cancer were assumed after the 4th year of the follow-up.

Methods used to judge relevance and validity, and for extracting data
The primary studies were identified selectively in order to include the most appropriate source of data. Specifically, the effects of treatment on the main outcome measures were obtained from a large randomised clinical trial, while long-term survival was derived from life tables relevant to the study context.

Measure of benefits used in the economic analysis
The summary benefit measures used were the quality-adjusted life-years (QALYs), life-years (LYs) and disease-free years (DFYs). The QALYs were estimated by combing survival data with quality of life (QoL) estimates derived from the literature, using data from patients with or without relapses and patients experiencing chemotherapy-related toxicity. The utility weights for patients with colorectal cancer were obtained using the health utility index 3. A weighted utility average of EQ-5D tariffs from the 1996 Health Survey for England was calculated for each year of follow-up using the estimated distribution by age and gender for patients alive and free of disease at the beginning of the year. The benefits were discounted at an annual rate of 3.5%.

Direct costs
The perspective of the NHS was adopted in the analysis of the costs. The analysis included the costs of chemotherapy, outpatient visits, laboratory tests, adverse events and surgery. The unit costs and the resource quantities were not presented separately. Resource use was estimated using data derived directly from the sample of patients enrolled in the MOSAIC study. The costs were estimated from different sources. The drug costs came from the British National Formulary, while the costs for physician consultations, imaging procedures, post-treatment procedures and surgical interventions for relapses were estimated using national reference costs. The costs of various laboratory tests were obtained from a personal communication with an expert in Newcastle. The costs were incurred during a long timeframe and discounting was applied at an annual rate of 3.5%. The price year was 2003.

Statistical analysis of costs
The costs appear to have been treated deterministically. However, bootstrapping was conducted to construct confidence intervals (CIs) around the total costs of the two alternative strategies.

Indirect Costs
The productivity costs were not considered.

Currency
UK pounds sterling (£).

Sensitivity analysis
A deterministic sensitivity analysis was performed to explore the impact of variations in clinical and economic
assumptions on the cost-utility ratios. The variables under examination were the length of follow-up in the trial, treatment regimens, utility estimates, discount rates, categories of costs, and the inclusion of both Stage II and Stage III patients. Finally, a bootstrap method was used to assess the impact of uncertainty surrounding efficacy and cost data from the MOSAIC trial.

### Estimated benefits used in the economic analysis

Over a 4-year time-horizon (trial-based analysis):

- The QALYs were 2.837 with OXA plus 5-FU/FA and 2.777 with 5-FU/FA alone (difference 0.060);
- The LYs were 3.439 with OXA plus 5-FU/FA and 3.384 with 5-FU/FA alone (difference 0.055); and
- The DFYs were 3.101 with OXA plus 5-FU/FA and 2.903 with 5-FU/FA alone (difference 0.198).

The long-term QALYs were 9.257 with OXA plus 5-FU/FA and 8.577 with 5-FU/FA alone (difference 0.680).

The long-term LYs were 11.739 with OXA plus 5-FU/FA and 10.971 with 5-FU/FA alone (difference 0.768).

The long-term DFYs were 11.153 with OXA plus 5-FU/FA and 9.906 with 5-FU/FA alone (difference 1.247).

### Cost results

The total costs per patient over the first 4 years were 3,407 greater for OXA plus 5-FU/FA than for 5-FU/FA alone. The difference was entirely due to the higher drug costs associated with OXA.

The long-term total costs (beyond 4 years) per patient were 1,352 with OXA plus 5-FU/FA and 1,491 with 5-FU/FA alone (difference -140).

Thus, the incremental cost predicted beyond 4 years for 5-FU/FA alone was small compared with the incremental cost of OXA plus 5-FU/FA over the first 4 years. The addition of OXA resulted in about 3,300 extra costs per patient.

### Synthesis of costs and benefits

Incremental cost-effectiveness and cost-utility ratios were calculated in order to combine the costs and benefits of the alternative strategies.

In the long-term analysis, the incremental cost per QALY gained with OXA plus 5-FU/FA over 5-FU/FA alone was 4,805 (95% CI: dominant to 45,658). The incremental cost per LY gained was 4,254 (95% CI: dominant to dominated). The incremental cost per DFY was 2,620 (95% CI: dominant to 8,108).

When the analysis was restricted to the 4-year time horizon, the incremental cost per QALY gained was 56,780, the incremental cost per LY gained was 61,942, and the incremental cost per DFY was 17,206.

The deterministic sensitivity analysis showed that base-case results did not change substantially.

More interesting results were observed in the bootstrapped analysis. Over the 50-year time horizon, OXA plus 5-FU/FA was both more effective and less costly than 5-FU/FA alone in 2.5% of replications. The probability of OXA plus 5-FU/FA being cost-effective over 5-FU/FA alone was 94.7% for a cost-effectiveness threshold of 20,000 per QALY gained and 96.7% for a threshold of 30,000 per QALY gained.

### Authors' conclusions

Oxaliplatin (OXA) plus 5-fluorouracil plus folinic acid (5-FU/FA) was a cost-effective adjuvant treatment for patients with advanced colon cancer. It was also pointed out that the cost-effectiveness of OXA plus 5-FU/FA compares favourably with other treatments currently accepted in the UK.
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. A description of the two alternative strategies was given, together with dosages and frequency of administration. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
Most of the effectiveness data were derived from a well-conducted clinical trial, which is usually a valid source of data. The large sample of patients included, the random allocation procedure, and the multi-centre nature of the trial ensure a high internal validity, which should have made the clinical estimates highly reliable. Data from the trial were then combined with published estimates of long-term survival and other assumptions made by the authors in order to evaluate the long-term impact of the treatments. Therefore, no systematic search for data was performed. The sensitivity analysis investigated the robustness of specific assumptions.

Validity of estimate of measure of benefit
Both disease-specific and generic measures of benefits were used. All of these were modelled using the extrapolation approach. LYs and QALYs have the advantage of being comparable with the benefits of other health care interventions. In particular, the use of QALYs was appropriate since the treatments under examination have a substantial impact on QoL. The instruments used to derive utility weights were described. Discounting was performed following UK guidelines, and the use of alternative discount rates was examined in the sensitivity analysis. The authors highlighted the issue of the limited availability of QoL values for patients with advanced colon cancer.

Validity of estimate of costs
The analysis of the costs was consistent with the perspective of the analysis. It appears that all the relevant categories of costs have been included. However, only macro-categories were presented and a detailed breakdown of the cost items was not given. This could limit the possibility of replicating the analysis in other settings. The sources of data were reported for each category of cost. In general, typical NHS sources were used. The use of alternative cost estimates was tested in the sensitivity analysis. The price year was reported, thus aiding reflation exercises in other time periods. The authors noted that the use of data on resource consumption from a clinical trial might lead to an overestimation of resources, owing to protocol-driven patient management. However, expert opinion was used to reflect current NHS treatment patterns.

Other issues
The authors stated that their findings were similar to those observed in other economic evaluations based on data from the MOSAIC trial. The issue of the generalisability of the study results to other settings was not explicitly addressed, although the sensitivity analysis investigated the use of alternative assumptions. The study referred to Stage III colon cancer patients and this was reflected in the authors’ conclusions.

Implications of the study
The study results support the use of OXA added to 5-FU/FA for the treatment of patients with Stage III colon cancer. The authors stated that ongoing trials are currently evaluating the use of OXA in combination with the oral form of 5-FU/FA (capecitabine) in the adjuvant setting.

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Bibliographic details
Other publications of related interest
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