A Markov model assessing the effectiveness and cost-effectiveness of FOLFOX compared with FOLFIRI for the initial treatment of metastatic colorectal 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.

CRD summary
This study compared two treatments, namely FOLFOX4 and FOLFIRI, for patients with metastatic colorectal cancer. The authors concluded that the two treatments were similar in their costs and effectiveness and that the incremental cost-effectiveness ratio for FOLFOX4 compared with FOLFIRI was below the accepted threshold of 100,000 US dollars per quality-adjusted life-year gained. Despite some limitations, the methods were valid and the authors’ conclusions appear to reflect the scope of their analysis.

Type of economic evaluation
Cost-utility analysis

Study objective
This study compared the cost-effectiveness of two treatments for patients with unresectable metastatic colorectal cancer.

Interventions
The interventions were the FOLFIRI regimen and the FOLFOX4 regimen. The FOLFIRI regimen consisted of irinotecan 180mg per m$^2$, on day one, with leucovorin 100mg per m$^2$ as a two-hour infusion, before 5-fluorouracil 400mg per m$^2$ administered as intravenous bolus injection, followed immediately by 5-fluorouracil 600mg per m$^2$ as a 22-hour infusion, on days one and two. The FOLFOX4 regimen consisted of oxaliplatin 85mg per m$^2$, on day one, with the same leucovorin and 5-fluorouracil regimen, on days one and two. For both regimens, patients received eight cycles of treatment, each of which lasted for two weeks.

Location/setting
USA/secondary care.

Methods
Analytical approach:
A Markov model was used to capture the progression of the condition. The time horizon was the patients’ life expectancy, with medical survival assumed to be less than two years in both groups (1.17 years with FOLFIRI and 1.25 years with FOLFOX4). The authors did not explicitly state the perspective adopted.

Effectiveness data:
The effectiveness data were mainly from a phase III multi-centre randomised controlled trial (RCT), which was augmented, where necessary, with data from published literature. The primary clinical outcomes included the probabilities of grade three-to-four neutropenia, febrile neutropenia, grade three-to-four diarrhoea, death, and death from FOLFIRI induced neutropenia.

Monetary benefit and utility valuations:
The utility values were from published literature.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the measure of benefit.

Cost data:
The direct costs were those associated with the management of grade three-to-four neutropenia, febrile neutropenia, grade three-to-four diarrhoea, and chemotherapy-induced diarrhoea. The costs of the chemotherapy regimens were also included. These costs were from national sources (Medicare and Medicaid). They were reported for the price year 2005 and were in US dollars ($).

Analysis of uncertainty:
Uncertainty was investigated, using a number of methods, including one-way sensitivity analysis on all the model parameters, threshold analysis on several key parameters, and probabilistic sensitivity analysis with 10,000 Monte Carlo simulations.

Results
The model found that the expected QALYs for FOLFOX4 were 1.003 and the expected costs were $29,865; the expected QALYs for FOLFIRI were 0.921 and the costs were $24,551.

An incremental analysis showed that compared with FOLFIRI, FOLFOX4 resulted in an incremental cost-effectiveness ratio (ICER) of $65,170 per QALY gained.

One-way sensitivity analyses demonstrated that the results were most sensitive to changes in the years of survival, the probability of death with FOLFOX4, and the cost of the chemotherapy regimens. Probabilistic sensitivity analysis demonstrated that the results were robust.

The FOLFOX4 regimen had a 52.72% probability of being more costly and more effective than FOLFIRI. Compared with FOLFIRI, FOLFOX4 had a 50.72% probability of having an ICER of less than $100,000 per QALY.

Authors’ conclusions
The authors concluded that the two regimens were quite similar in their effectiveness and costs, and the ICER of FOLFOX4 compared with FOLFIRI was below $100,000 per QALY.

CRD commentary
Interventions:
The interventions were described in detail, with their doses, but it was not clear that all the relevant treatment options were considered.

Effectiveness/benefits:
No systematic search of the literature was reported, which makes it difficult to assess if the best available evidence was considered. In general, a RCT is an appropriate source for the clinical data, given the strengths of this design. The details, such as the inclusion and exclusion criteria, randomisation procedures, power calculations to ensure an appropriate sample size, and the method of analysis of the clinical data, were not reported, which makes it difficult to assess the internal validity of the data. QALYs were an appropriate measure, because they not only synthesise the quantity and quality of life, but also allow for cross-disease comparisons. The methods used to derive the utilities were not reported and an assessment of their validity and appropriateness cannot be made.

Costs:
The perspective was not explicitly reported, but it appears to have been that of the third-party payer. The unit costs and resource quantities were not reported separately, with costs reported only as total categories. The lack of detail on the resources used might limit the generalisability of the analysis. The sources of the costs and the price year were reported, aiding future reflation exercises.

Analysis and results:
The model structure was clearly described and presented in a diagram. The costs and benefits were appropriately synthesised, using an incremental approach. The issue of uncertainty was adequately addressed, using a deterministic as
well as a probabilistic approach. The results of the base case and all the sensitivity analyses were presented appropriately. The authors briefly discussed some limitations to their study and these mainly related to the sources for the effectiveness data and the modelling assumptions.

Concluding remarks:
Despite some limitations, the methods were valid and the authors’ conclusions appear to reflect the scope of their analysis.

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