Cost-effectiveness projections of oxaliplatin and infusional fluorouracil versus irinotecan and bolus fluorouracil in first-line therapy for metastatic colorectal carcinoma

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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 use of oxaliplatin and infusional fluorouracil (FU) (FOLFOX) as first-line therapy for patients with metastatic colorectal cancer (CRC). The FOLFOX regimen evaluated was oxaliplatin 85 mg/m2 on day 1, and bolus FU 400 mg/m2 plus leucovorin (LV) 200 mg/m2 followed by FU 600 mg/m2 in 22-hour infusions on days 1 and 2 every 2 weeks.

Type of intervention
Treatment.

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

Study population
The study population comprised patients aged over 18 years with newly diagnosed metastatic CRC. The inclusion and exclusion criteria were derived from the primary clinical trial.

Setting
The study was conducted in an outpatient setting. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were derived from a study published in 2004. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that included in the clinical trial.

Study sample
Limited information on the primary trial was reported in the current economic evaluation. The study sample comprised 264 patients in the IFL group and 267 patients in the FOLFOX group. The median age was 61 years for both groups. The proportion of females was 39% in the IFL group and 41% in the FOLFOX group.

Study design
This was a prospective, randomised clinical trial that was carried out at five centres in the USA. Patients were enrolled between May 1999 and April 2001. The median length of follow-up was 3 years. No information on loss to follow-up was provided. Blinding was not performed.

Analysis of effectiveness
The outcomes estimated in the clinical trial were transformed into probability values required to populate the decision model. These were:

- the daily probability of transition from well to progression, and from progression to death with IFL;
- the rate of daily toxic death in the first 60 days with IFL;
- the corresponding risk reductions with FOLFOX; and
- the percentage of delays or deferrals in first-line treatment if progression-free.

Adverse events with FOLFOX and IFL were also reported. In addition, the patients’ quality of life was assessed using three different measures (a single-item scale, a 12-item symptom distress scale and a symptom-specific scale). These quality of life assessments were performed every 12 weeks and had a 75% completion rate. The two groups were well-balanced in terms of their demographics and other baseline characteristics.

Effectiveness results
With IFL, the daily probability of transition from well to progression was 3.1 x 10^-3, the daily probability of transition from progression to death was 4.1 x 10^-3, and the rate of daily toxic death in the first 60 days was 8.5 x 10^-4.

With FOLFOX, the relative risk reduction in the transition from well to progression was 0.74 (range: 0.61 to 0.89), the relative risk reduction in the daily probability of transition from progression to death was 0.83 (range: 0.83 to 1.0), and the relative risk reduction in the rate of daily toxic death in the first 60 days was 0.55 (range: 0.55 to 1.0).

The percentage of delays or deferrals in first-line treatment if progression-free was 77% with FOLFOX and 85% with IFL during cycles in months 2 to 6. It was 50% with both regimens in months 6 to 12.

Grade 5 fatal toxicity occurred in 2.6% of patients receiving FOLFOX and 4.6% of patients receiving IFL.

The most common adverse events for the IFL group were diarrhoea (17.8%), volume depletion (10.8%) and nausea (8.9%). The most common adverse events for the FOLFOX group were diarrhoea (10.5%), pneumonia (8.6%) and volume depletion (7.0%).

The two groups had similar quality of life scores.

Clinical conclusions
The effectiveness results were used as model inputs.

Modelling
A Markov model was constructed to simulate the clinical and economic consequences of the two first-line chemotherapy regimens in patients with metastatic CRC. Patients moved to alternative health states on a daily basis until death. Alternative health states were hospitalisation, stable or responding metastatic CRC, treatment-associated death, progression of metastatic CRC, second-line chemotherapy and palliative care. Treatment complications leading to death were considered in the first 60 days, while those leading to hospitalisation were considered in the first 6 months. Treatment was not stopped for nonfatal treatment complications. Patients with progression of their metastatic CRC could either receive or not receive second-line chemotherapy. The time horizon of the model was 5 years. A graphical representation of the model was reported.
Methods used to derive estimates of effectiveness
Some experts’ opinions were used to derive some clinical data that were not directly available from the trial.

Estimates of effectiveness and key assumptions
Benefits and risks were expressed as relative risks that were constant over time (i.e. the daily probability of progression during first-line therapy was constant).

The percentage of delays or deferrals in first-line treatment if progression-free was 15% with FOLFOX and 25% with IFL during the period 12 to 17.9 months. It was 1% with both drugs after 18 months.

The proportion of semi-permanent venous access prior to treatment was 100% in FOLFOX patients and 30% in IFL patients.

Measure of benefits used in the economic analysis
The summary benefit measure used was the expected survival. This was estimated using a modelling approach. Quality-adjusted life-years (QALYs) were also calculated by attributing a utility score to the model health states. Utility weights were obtained from a published study that used the rating scale. Given that rating scales tend to underestimate quality of life scores for health states, the utility weights were multiplied by 1.07. Survival and QALYs were discounted at an annual rate of 3%.

Direct costs
The analysis of the costs was performed from the perspective of the third-party payer. It included the costs of drugs, chemotherapy administration, diagnostic work-up, treatment of complications, second-line therapy and palliative care. Extensive information on resource use and quantities of resources used was provided, especially with respect to chemotherapy doses. All the assumptions made to assess resource use were explicitly reported. The costs were derived from Medicare national average reimbursement rates for physicians and treatment administration. The 2003/04 billing records of 30 patients in the Virginia Commonwealth University Health System who had received either IFL or FOLFOX for CRC were reviewed. Resource use was derived from data collected prospectively alongside the clinical trial. Discounting was relevant given the 5-year time horizon of the analysis and an annual discount rate of 3% was used. The price year appears to have been 2004.

Statistical analysis of costs
Statistical analyses of the costs were not performed.

Indirect Costs
Indirect costs were not relevant given the perspective of the study.

Currency
US dollars ($).

Sensitivity analysis
An extensive sensitivity analysis was carried out to assess the robustness of the cost-effectiveness ratios to variations in the clinical and economic inputs used in the decision model. The data varied were the effectiveness of FOLFOX, dosages and patterns of second-line regimens, economic impact of palliative care, use of semi-permanent venous access procedure, use of progression-free survival as benefit measure, 3-year time horizon, treatment duration and drug costs. Alternative ranges of values were generally derived from published sources or from 95% confidence intervals in the primary trial.
Estimated benefits used in the economic analysis
Over 5 years, the expected survival was 19.8 months with FOLFOX and 15.4 months with IFL (difference 4.4 months or 0.37 years).

The incremental QALYs for FOLFOX over IFL over a 5-year time horizon were 0.26.

Cost results
The total costs per patient over 5 years were $94,693 with FOLFOX and $66,231 with IFL (difference $29,523). The difference was mainly due to the higher drug costs for FOLFOX.

Synthesis of costs and benefits
An incremental analysis was carried out to combine the costs and benefits of the alternative strategies.

The incremental cost per life-year gained with FOLFOX over IFL was $80,407.

The sensitivity analysis showed that the incremental cost per life-year saved ranged from $59,250 to $222,200, the lowest value being achieved with the upper bound of the relative efficacy of FOLFOX over IFL. Quality of life adjustments increased the cost-effectiveness ratio, as did the use of a shorter timeframe and the use of progression-free survival as a summary benefit measure. The incremental cost per QALY for FOLFOX over IFL was $111,890, and the incremental cost per progression-free year was $89,080.

Longer treatment duration was associated with a higher cost-effectiveness ratio. In general, changes in other inputs did not substantially alter the conclusions of the analysis. A threshold analysis on the price of drugs showed that, at thresholds of $20,000 and $50,000 per life-year, the price of oxaliplatin would have to decrease by 76% and 38%, respectively, to fall below these thresholds.

Authors’ conclusions
The use of oxaliplatin and infusional fluorouracil (FOLFOX) for the treatment of patients with colorectal carcinoma (CRC) improved patient survival at substantial additional costs from the perspective of the third-party payer in the USA. However, the estimated cost-effectiveness ratio “fell into the upper range of commonly accepted oncology interventions”.

CRD COMMENTARY - Selection of comparators
The authors justified their choice of the comparators. Three regimens were compared in the primary trials, namely IFL, FOLFOX, and irinotecan and oxaliplatin (IROX). IROX was not considered because it was not a reference standard (and was not the superior arm in the trial). You should decide whether these are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a clinical trial, which was appropriate for the study question. The use of a randomised design should reduce the potential impact of selection bias. A large sample of patients was enrolled, which enhances the robustness of the comparison. Further advantages were the multi-centre design and the appropriate length of follow-up. These issues should have had a positive impact on the robustness of the study. However, the primary trial had already been published in a separate article, so only limited details on the design and other aspects of the study were reported in the current economic evaluation. The impact of some of the clinical estimates used in the model on the results of the analysis was investigated in the sensitivity analysis. However, the main assumption about the duration of the treatment effect was not tested.

Validity of estimate of measure of benefit
The use of survival as the summary benefit measure was appropriate since life-years capture the most relevant dimension of health for patients with CRC. The use of utility weights showed that the impact of quality of life was not relevant. Further, the authors stated that quality of life end points used in the primary trial were comparable between treatment arms. Discounting was performed, as recommended by US guidelines. A further advantage of life-years is the fact that they can be compared with the benefits of other health care interventions.

Validity of estimate of costs
The analysis of the costs was consistent with the perspective adopted. The authors did not include the indirect costs, stating instead that the inclusion of such costs would probably not have altered the results of the analysis. Extensive information on the unit costs and quantities of resources used was presented, which will help in replicating the analysis in other settings. The costs were calculated using a modelling approach. Resource consumption was based on data derived from the clinical trial. The sources of the costs reflected the perspective of the study. The cost estimates were specific to the study setting, but the impact of using alternative cost estimates was investigated in the sensitivity analysis. The price year was implicitly stated, which will facilitate reflation exercises in other settings. The authors explicitly reported the assumptions made in the calculation of the total costs.

Other issues
The authors made only limited comparisons of their findings with those from other studies. They did not explicitly address the issue of the generalisability of the study results to other settings. However, the extensive use of sensitivity analysis enhances the external validity of the study. The author highlighted the high uncertainty around the size of benefit with FOLFOX and its strong impact on the cost-effectiveness results. Given the uncertainty around this model parameter, a probabilistic sensitivity analysis might have provided additional information of interest for decision-makers. The study referred to patients with CRC and this was reflected in the authors' conclusions.

Implications of the study
The study results suggest that FOLFOX may be a cost-effective chemotherapy regimen for patients with CRC.

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