Cetuximab in the treatment of metastatic colorectal cancer: a model-based cost-effectiveness analysis
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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 the combination of cetuximab and irinotecan as third-line treatment for metastatic colorectal cancer (mCRC). This chemotherapy strategy was compared with current standard treatment, which usually consists of follow-up (no third-line chemotherapy). An initial dose of 400 mg/m² cetuximab intravenously was followed by 250 mg/m² weekly until disease progression (median treatment duration between 2.9 and 4.1 weeks).

Type of intervention
Palliative care.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with mCRC requiring third-line chemotherapy.

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

Dates to which data relate
The clinical data and some information on resource use were derived from studies published between 2001 and 2004. The price year was 2005.

Source of effectiveness data
The clinical data used in the decision model were the response rates (partial and complete response) with combined therapy, time to disease progression and survival rates.

Modelling
The author stated that a simple decision model was constructed to assess the cost-effectiveness of the combined third-line chemotherapy strategy (cetuximab-irinotecan) in comparison with conventional care. The patients were followed until death. However, no details of the model were reported and it is likely that a simple algorithm was applied to obtain the costs and effects associated with the treatments compared.

Sources searched to identify primary studies
The clinical data were derived from a randomised study that compared cetuximab-irinotecan with cetuximab alone, and three single-arm phase II/III studies that included cetuximab-irinotecan (1 study) or cetuximab alone (2 studies). The
Methods used to judge relevance and validity, and for extracting data
Primary studies were identified through a systematic review of the literature carried out by searching MEDLINE (January 2005) and the abstracts of the 2004 meeting of the American Society of Clinical Oncology. Only four studies were found and used as sources of data. However, much of the data used in the analysis were taken from the randomised clinical trial and no data synthesis was conducted.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic evaluation was the number of life-years (LYs) gained with the combined cetuximab-irinotecan therapy over standard care. The LYs were derived directly from the review of the literature. No discounting was performed as an average short-term survival was used.

Direct costs
The viewpoint of the analysis was that of a third-party payer. The analysis included the costs associated with drugs (cetuximab, irinotecan and ondansetron), assessment of epidermal growth factor receptor (EGFR) status (which was investigated by immunohistochemistry, IHC), hospitalisations, outpatient visits and patient/family travel. The unit costs and the quantities of resources used were presented separately for some items. The drug costs came from the pharmacy at the University Hospital of North Norway in Tromso, Norway. Other health care service costs came from a national price list covered by the National Insurance Administration. Travel costs were paid by the hospital and were based on a national tariff using a mean distance. Data on resource use were mainly derived from the same studies as those used to derive some clinical data. Discounting was not relevant as the costs were incurred during a short time period, owing to the poor survival of the patients. The price year was 2005.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
Productivity costs were not included as patients with mCRC usually do not return to the work force.

Currency
Norwegian kroner (NOK). These were converted into euros (EUR) at the rate EUR 1 = NOK 8.78.

Sensitivity analysis
A univariate sensitivity analysis was performed to evaluate the impact of individual model inputs on the cost-effectiveness ratios. The model parameters under examination were assumptions about IHC analysis for EGFR expression, the costs of outpatient treatment, pharmacy administration costs, drug costs (cetuximab and irinotecan) and expected survival. Alternative values for the IHC analysis were derived from the literature. The author defined other values (25% or 50%).

Estimated benefits used in the economic analysis
The expected survival gained with cetuximab over standard therapy ranged from 1.7 to 2.0 months depending on the source used.

Cost results
The expected incremental cost of cetuximab in comparison with conventional therapy ranged from EUR 34,256 to EUR 45,764, depending on the assumptions around time on therapy (cycles and weeks of administration).

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios (ICERs; i.e. the additional cost per LY gained) were calculated in order to combine the costs and benefits of the alternative strategies.

The ICER with cetuximab over standard care ranged from EUR 205,536 to EUR 323,040, depending on the source used to derive LYS and time on therapy.

The sensitivity analysis indicated that the cost of cetuximab and survival gain had the greatest impact on the ICERs. Clearly, reductions in the drug price or dose reductions led to savings in total costs. However, the cost of cetuximab would need to be reduced by 90% to obtain an incremental cost per LYS gained of lower than EUR 50,000 compared with standard care.

**Authors’ conclusions**
The combined chemotherapy regimen of cetuximab and irinotecan was an effective third-line therapy for patients with metastatic colorectal cancer (mCRC), but the high drug costs did not make the combination strategy attractive in comparison with conventional care (follow-up without third-line treatment).

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators was clear as the proposed chemotherapy strategy was compared with the conventional approach for patients with mCRC. Dosages were clearly reported. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The clinical data were derived from a review of the literature, the methods and conduct of which were described. The search strategy, including keywords, was reported. Details of the design and characteristics of the patient samples were given. Only one randomised study, a design usually associated with a high internal validity, was included. However, the author acknowledged that this trial had some limitations, such as the small sample size and the high number of crossover between arms. The other primary sources were non-randomised studies. The key clinical parameters were tested in the sensitivity analysis, but only a univariate analysis was performed and no justification for the ranges of variations was given.

**Validity of estimate of measure of benefit**
The use of LYSs as the summary benefit measure was appropriate, not only because survival represents the most relevant outcome of a chemotherapy programme, but also because LYSs can be compared with the benefits of other health care interventions.

**Validity of estimate of costs**
The costs included were consistent with the perspective of the analysis. The author justified the exclusion of productivity costs. Some information on the unit costs and quantities of resources used was given, which enhances the possibility of replicating the analysis in other settings. The sources of the costs were reported. No statistical analyses of the cost estimates were performed, but the impact of changing some key costs was investigated in the sensitivity analysis. The author reported the price year, which will simplify reflation exercises in other time periods. The decision not to carry out discounting was appropriate given the short timeframe of the analysis.

**Other issues**
The author did not make extensive comparisons of his findings with those from other studies. The issue of the generalisability of the study results to other settings was also not explicitly addressed. However, the use of some sensitivity analysis enhances, to some extent, the external validity of the analysis. The author discussed the issue of the limited published evidence on the cost-effectiveness of cetuximab and focused on the critical issue of defining a
conventional threshold for ICER in oncology. In general, however, the main limitations of this economic evaluation appear to be the poor clinical evidence and the methods used to deal with parameter uncertainty.

Implications of the study
The study results cast some doubts on the cost-effectiveness of cetuximab-irinotecan as a third-line chemotherapy option for patients with mCRC. Reductions in drug prices or increases in survival gains might support the use of this chemotherapy regimen.

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MeSH
Adult; Aged; Aged, 80 and over; Antibodies, Monoclonal /economics /therapeutic use; Antibodies, Monoclonal, Humanized; Antineoplastic Combined Chemotherapy Protocols /economics /therapeutic use; Camptothecin /administration & dosage /analogs & derivatives /economics; Cetuximab; Clinical Trials as Topic; Colorectal Neoplasms /drug therapy /economics /pathology; Cost-Benefit Analysis; Humans; Middle Aged; Models, Theoretical; Neoplasm Metastasis /drug therapy; Sensitivity and Specificity

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