Cost-effectiveness analysis of KRAS testing and cetuximab as last-line therapy for 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 investigated the cost-effectiveness of Kirsten rat sarcoma viral oncogene homologue (KRAS) testing before cetuximab or best supportive care as the last-line treatment for patients with metastatic colorectal cancer. The authors concluded that KRAS testing was recommended rather than cetuximab for all patients, but cetuximab with or without testing was not cost-effective. One or two aspects of the analysis were not well reported, but the conclusions reached by the authors appear to be reasonable.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
The aim was to examine the costs and health outcomes of Kirsten rat sarcoma viral oncogene homologue (KRAS) testing prior to cetuximab as the final treatment option for colorectal cancer. The hypothetical cohort consisted of adults with metastatic colorectal cancer, who had received chemotherapy, which had failed, or who had contraindications for chemotherapy. Each adult was assumed to have a body surface area of 1.7m$^2$ and 40% of them were assumed to have a mutated KRAS gene.

Interventions
The three strategies were cetuximab for all patients without testing, best supportive care (BSC) for all patients without testing, and testing for KRAS mutations, with cetuximab for those without the mutation and best supportive care (BSC) for those with the mutation. The dose of cetuximab was 400mg per m$^2$ of body surface area on day one, followed by 250mg per m$^2$ once weekly.

Location/setting
Japan/secondary care.

Methods
Analytical approach:
A Markov model was used to combine published data for the progression of colorectal cancer until death. The time horizon was 2.5 years. The authors stated that they took a Japanese health care payer's perspective.

Effectiveness data:
The key clinical outcomes were progression-free survival and overall survival. These data and the probabilities of transition from progression-free survival to disease progression were based on survival curves from the National Cancer Institute of Canada (NCIC) Clinical Trials Group CO.17 trial (Karapetis, et al. 2008, see 'Other Publications of Related Interest' below for bibliographic details). A Japanese Ministry of Health report was used to estimate the probability of progression-free survival until death.

Monetary benefit and utility valuations:
The utility estimates were from a cost-effectiveness study of KRAS testing and cetuximab.

Measure of benefit:
The measures of benefit were quality-adjusted life-years (QALYs) and life-years saved (LYS). These were discounted.
Cost data:
The direct medical costs included medications, out-patient chemotherapy, disease monitoring (blood and biochemical tests, and scans) and pharmacy fees. The cost of BSC was based on daily opioid treatment. Terminal care was assumed to be the same for all three groups and omitted. Compliance with drugs was not included as adherence was found to be very high in a previous study. The unit costs and resources were provided and were based on social insurance reimbursements and national drug tariffs. Costs were presented in 2010 Japanese yen (JPY) and US dollars ($), using an exchange rate of $1 equals JPY 90. They were discounted annually at 3%.

Analysis of uncertainty:
One-way sensitivity analyses were performed on the key parameters; the discount rate, the body surface area, the percentage of patients with a KRAS mutation, the BSC costs, the survival hazard ratios, and the testing costs. A probabilistic sensitivity analysis used gamma distributions for the disutility values and normal distributions for the costs. The results were presented in tables and a cost-effectiveness acceptability frontier.

Results
Over 2.5 years, the total discounted costs were JPY 2.6 million ($29,000) for KRAS testing, JPY 3.16 million ($35,000) for cetuximab, and JPY 0.62 million ($6,800) for BSC. The total QALYs gained were 0.49 for KRAS testing, 0.48 for cetuximab, and 0.36 for BSC.

Compared with BSC, the incremental cost per QALY gained was JPY 16 million ($180,000) with KRAS testing, and JPY 21 million ($230,000) with cetuximab. KRAS testing was dominant over cetuximab as it was less costly and produced more QALYs.

The one-way sensitivity analyses showed that variations in the key parameters did not markedly alter these results. At a willingness-to-pay threshold of JPY 5 million per QALY gained, KRAS testing was not cost-effective in any simulations. At a threshold of JPY 10 million per QALY gained, it was cost-effective in 19% of simulations.

Authors’ conclusions
The authors concluded that for patients with metastatic colorectal cancer, KRAS testing was recommended rather than administering cetuximab to all patients, but cetuximab with or without testing was not cost-effective, compared with best supportive care, even if treatment was limited to patients with the wild-type KRAS mutation.

CRD commentary
Interventions:
A good description of KRAS testing, cetuximab, and best supportive care was provided. Cetuximab may be available and accessible to patients with metastatic colorectal cancer in other settings.

Effectiveness/benefits:
Details of randomisation, the participants, and clinical care in the pivotal trial were not provided, and the original publication should be consulted to assess its internal validity (Karapetis, et al. 2008). The survival curves were not described. Graphs were presented and it seems that different functional forms were used for different curves, one of them being a two-step form; the model fit and the uncertainty in the parameters was not described. Conservative utility values were used and they were varied in a sensitivity analysis, which did not alter the conclusions. How these utilities were measured and valued was not described and there was no indication that a utility value was given to the disease-progression health state.

Costs:
The resource quantities and unit costs were clearly presented. Normal distributions were assumed for the costs in the probabilistic sensitivity analysis, where usually gamma or log-normal distributions are used. The unit costs were from publicly available national sources.

Analysis and results:
The authors compared their findings with those of other studies on cetuximab, which did not include KRAS testing.
The findings of these studies in other settings were consistent with these findings that cetuximab for metastatic colorectal cancer was not cost-effective. The results of the sensitivity analyses were fully reported. The uncertainty was evaluated in probabilistic sensitivity analysis, with limited reporting of the uncertainty in the individual parameters. Some limitations were acknowledged in the report including the assumptions made when deriving the BSC costs, but variations in these had no major impact on the results.

Concluding remarks:
There were one or two aspects of the analysis that were not well reported, but the conclusions reached by the authors appear to be reasonable.

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