Cost-effectiveness of cetuximab, cetuximab plus irinotecan, and panitumumab for third and further lines of treatment for KRAS wild-type patients with metastatic colorectal cancer

Hoyle M, Peters J, Crathorne L, Jones-Hughes T, Cooper C, Napier M, Hyde C

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
The study objective was to assess the cost-effectiveness of cetuximab, cetuximab plus irinotecan and panitumumab for third and subsequent line treatment of colorectal cancer. The authors concluded that all three treatments were highly unlikely to be cost-effective. Overall the reporting and methodology were satisfactory. The authors' conclusion appears to be appropriate.

Type of economic evaluation
Cost-utility analysis

Study objective
The study objective was to assess the cost-effectiveness of cetuximab, cetuximab plus irinotecan, and panitumumab for third and subsequent line treatment of colorectal cancer. The study population was patients with Kirsten rat sarcoma (KRAS) wild-type metastatic colorectal cancer.

Interventions
Three interventions were assessed: cetuximab (mean dose 511mg); cetuximab plus irinotecan (mean dose irinotecan 352mg); and panitumumab (mean dose 499mg). The comparator was best supportive care (BSC). Each treatment was considered as a third or subsequent line of treatment. All patients had previously taken irinotecan and most had previously taken oxaliplatin.

Location/setting
UK/secondary care

Methods
Analytical approach:
A Markov model was constructed to estimate the cost-effectiveness of the treatment options over 10 years. The authors stated that the analysis was conducted from the perspective of the UK National Health Service and Personal Social Services.

Effectiveness data:
The key effectiveness data was the progression free survival and overall survival. A systematic review was undertaken to identify the effectiveness evidence. One randomised controlled trial (RCT) was identified for cetuximab and panitumumab each for the KRAS population. For cetuximab plus irinotecan the one RCT identified did not have KRAS status as an inclusion criteria, and two observational studies were used to adjust the estimates.

The relative treatment effects were obtained from an indirect comparison of the pairwise effect estimates. Survival curves were used to determine the number of patients in progression free survival or overall survival at any time, and the time in the progressed disease state was calculated as overall survival-progression free survival. The mean overall survival for BSC in the panitumumab versus BSC RCT was reduced to allow for the substantial crossover of patients from BSC to panitumumab.

Monetary benefit and utility valuations:
Treatment specific utility values were assigned to the three model health states: progression free survival, progressed...
disease state and death. Most values were obtained directly from Merck Serono (the manufacturer of cetuximab), using mostly RCT data as the sources. Adjustments were made by the authors to bring Merck Serono's estimates in line with general population values, maintain consistency or comply with the authors' assumptions.

Measure of benefit:
The health benefit was measured in quality-adjusted life-years (QALYs). Future benefits were discounted at a rate of 3.5% per annum.

Cost data:
Direct costs were included in the analysis. The cost items included drug acquisition and delivery, KRAS testing, outpatient visits, scans, BSC in progressed disease state and adverse event treatment. Costs were estimated using NHS Reference Costs 2008-9, Merck Serono values, British National Formulary (BNF) 63 and authors’ assumptions. Treatment duration was estimated using RCT data, personal communication and authors’ assumptions. In the calculation of the cost of KRAS testing, it was assumed that 54% of patient were KRAS wild-type (informed by Merck Serono). Costs were reported in 2011-2012 GBP (£) and were inflated where necessary. Future costs were discounted at an annual rate of 3.5%.

Analysis of uncertainty:
One way sensitivity analysis and probabilistic sensitivity analysis were conducted. A cost-effectiveness acceptability curve (CEAC) was produced, which shows the probability that each alternative was cost-effective at different willingness to pay (per additional QALY) thresholds.

Results
Over 10 years cetuximab produced 0.6 QALYs and cost £28,860; panitumumab produced 0.52 QALYs and cost £35,213; cetuximab plus irinotecan produced 0.97 QALYs and cost £62,560. Compared to BSC, the incremental cost-effectiveness ratio (ICER) was £90,000 per QALY for cetuximab, £187,000 per QALY for panitumumab, and £88,000 per QALY for cetuximab plus irinotecan. Cetuximab dominated panitumumab (producing more QALYs and costing less). Cetuximab was extendedly dominated by cetuximab plus irinotecan, and BSC (with cetuximab having a higher incremental cost-effectiveness ratio (ICER)).

In the one-way deterministic sensitivity analyses the ICERs all remained high. The CEAC showed that cetuximab and panitumumab were never predicted to be the most cost-effective options (up to a £140,000 threshold). Up to a threshold around £85,000 per QALY BSC was likely to be the most cost-effective treatment; over £85,000 cetuximab plus irinotecan was most likely to be the most cost-effective alternative.

Authors’ conclusions
The authors concluded that all three treatments were highly unlikely to be cost-effective.

CRD commentary
Interventions:
Brief details of the interventions were reported. An appropriate comparator (best supportive care) was used in the analysis, but specific details on what BSC consisted of were not reported. The authors mentioned that bevacizumab was an alternative targeted agent. The authors did not justify the exclusion of this alternative from the analysis. The reader should consider whether or not all alternatives relevant to their setting have been included in the analysis.

Effectiveness/benefits:
A systematic review was conducted to identify evidence, however the authors did not report how evidence was selected (i.e. the inclusion criteria) so it was unclear if all relevant evidence was included in the indirect comparison.

An indirect comparison was conducted to derive the effectiveness estimates, and an appropriate method was used. The authors stated that the results for cetuximab versus BSC were likely to be relatively accurate, because the clinical data was taken from a high quality RCT. The results for panitumumab versus BSC were stated to be less certain due to assumptions in the adjustment for the substantial crossing-over of patients in the RCT. The results for cetuximab plus irinotecan versus BSC were stated to be least certain due to substantial uncertainty around the effectiveness estimates. The cetuximab plus irinotecan RCT population was not quite the same and the estimate had to be adjusted. Otherwise
the patient characteristics were similar across the trials.

Since the utility values were estimated using RCT data for each of the treatments it may be assumed that appropriate populations were used to derive the values. The tool used to measure utilities was not reported.

Costs:
The authors indicated that the estimate for treatment duration for cetuximab plus irinotecan was subject to substantial uncertainty. Given that other treatment duration estimates were derived using personal communication and authors' assumptions, these were likely to be subject to uncertainty also. Appropriate cost adjustments were conducted. The costs were specific to UK. The costs were generally appropriate for the study population, except that the cost of medical management for progressed disease state was taken from a study of UK patients with breast cancer. The authors assumed that resources to alleviate pain and other symptoms once off active drug treatment would be similar across cancer types, which seems reasonable.

Analysis and results:
The model was clearly described. The authors justified the choice of time horizon, stating that most people had died at 10 years. The results of the main analysis were clearly reported. Appropriate sensitivity analyses were conducted to assess the level of uncertainty around the results. Only partial results for the deterministic sensitivity analyses were reported; clearer reporting of all the results would have allowed a more comprehensive analysis of the key parameters driving uncertainty around the results. For the probabilistic analysis the parameters included and distributions applied were not reported. It was unclear whether the analysis was appropriate. Nevertheless given the magnitude of the ICER results the authors' conclusion appears to be appropriate.

Concluding remarks:
Overall the reporting and methodology were satisfactory. The authors' conclusion appeared to be have been appropriate.

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