Costs of trastuzumab in combination with chemotherapy for HER2-positive advanced gastric or gastroesophageal junction cancer: an economic evaluation in the Chinese context

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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 the addition of trastuzumab to conventional chemotherapy, for patients with human epidermal growth factor receptor 2-positive advanced gastric or gastro-oesophageal junction cancer, in China. The authors concluded that the addition of trastuzumab was not cost-effective, for the Chinese health system, at the time. Despite limited available data, hence high levels of uncertainty, the methods of the study were appropriate. The authors’ conclusion is a reasonable reflection of the analysis undertaken.

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

Study objective
The aim was to assess the cost-effectiveness of adding trastuzumab to standard chemotherapy for a hypothetical population of patients with human epidermal growth factor receptor 2 (HER2)-positive, advanced gastric or gastro-oesophageal junction cancer, in China. The average patient weight was 65kg, height was 1.64m, and body surface area was 1.72m².

Interventions
Six three-week chemotherapy cycles were administered. Standard chemotherapy was capecitabine (1g per m², twice daily, on days one to 14) or fluorouracil (800mg per m², intravenously, on days one to five) plus cisplatin (80mg per m², intravenously, on day one). Trastuzumab was administered at a dose of 8mg per kg on day one, followed by 6mg per kg, every three weeks. If disease progressed, patients were given paclitaxel (80mg per m², per week, every four weeks).

Location/setting
China/out-patient care.

Methods
Analytical approach:
A Markov model used published data to simulate the progression of patients receiving each of the treatments. The time horizon was five years, which was two years beyond the end of the key trial. The authors stated that the perspective was that of the Chinese health system.

Effectiveness data:
The effectiveness of trastuzumab was estimated using progression-free survival and overall survival. These data were from a three-year randomised controlled trial – Trastuzumab in Combination with Chemotherapy versus Chemotherapy Alone for Treatment of HER2-Positive Advanced Gastric or Gastro-Oesophageal Junction Cancer (ToGA) trial (see Other Publications of Related Interest). Weibull survival models were fitted to the data from the ToGA trial and Kaplan-Meier survival curves extrapolated the data to five years. Grades three and four adverse events, and the data to derive the model transition probabilities, were from the ToGA trial.

Monetary benefit and utility valuations:
The health state valuations were from a published study, and were estimated for the two alive health states of progression-free survival and progression. The utility values were measured, using the time trade-off approach, with gastric cancer patients, whose characteristics were similar to those of patients in the ToGA trial.
Measure of benefit:
The measures of benefit were life-years saved, and quality-adjusted life-years (QALYs). Discounting was applied at an annual rate of 3%.

Cost data:
The direct medical costs were included for trastuzumab and chemotherapy administration and supportive care, the treatment of severe adverse events (grade three or four), physician visits, imaging, and monitoring. Patient-level data on resource use were obtained from the ToGA trial. The unit costs were from local health systems or the National Development and Reform Commission of China. The costs were discounted at 3% and reported in 2010 US $.

Analysis of uncertainty:
One-way sensitivity analyses were performed on most inputs, using 95% confidence intervals, where available. The uncertainty was assessed in probabilistic sensitivity analysis, with log-normal distributions for the costs and beta distributions for the utilities and probabilities. The results were presented in a scatterplot on the cost-effectiveness plane, and in cost-effectiveness acceptability curves.

Results
For trastuzumab plus chemotherapy, the mean discounted costs were $54,433 and the discounted QALYs were 1.02. For chemotherapy alone, the mean discounted costs were $6,443 and the discounted QALYs were 0.83.

The incremental cost was $46,990 and the incremental QALYs were 0.18 QALYs (approximately two months quality-adjusted survival). Over five years, the incremental cost per QALY gained was $250,163. The incremental cost per life-year saved was $213,592.

Varying the model parameters showed that the incremental cost per QALY ratio was most sensitive to the median overall survival with either treatment, the median progression-free survival with chemotherapy, the proportion of patients using capecitabine, and the cost of trastuzumab per 440mg.

Authors’ conclusions
The authors concluded that the addition of trastuzumab to conventional chemotherapy, for patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer, was not cost-effective at the threshold used at the time, in China.

CRD commentary
Interventions:
The authors chose trastuzumab plus usual chemotherapy versus chemotherapy alone as the two comparators. The dosages and average patient weight were clearly stated. The authors acknowledged that these were only two of the potential comparators; the inclusion of other comparators would alter the incremental cost-effectiveness ratio.

Effectiveness/benefits:
The efficacy and health state transition parameters were from the pivotal ToGA trial, and this trial should be assessed to determine the internal validity of the clinical estimates. The ToGA trial was open label and could be subject to bias or contamination of treatment arms, making it difficult to judge the true benefit of trastuzumab. The sensitivity analysis highlighted the importance of addressing the uncertainty in the survival data. Digitised Kaplan-Meier median survival was used, rather than mean survival, and the data were extrapolated, so further investigation is warranted. The utility values were extracted directly from a study of other patients with gastric cancer, and the sample and valuation methods were briefly reported. How this source study was identified and selected, was not reported, and a comprehensive review of the utility literature could have reduced the high uncertainty in the estimates used.

Costs:
The perspective was that of the Chinese health system and all the relevant direct medical costs appear to have been included, as well as those of the major adverse events. The resource use was from national sources, and patient-level hospitalisation data. The results of the one-way and probabilistic sensitivity analyses were clearly reported. It was clear to what extent each individual cost and effect variable influenced the incremental cost per QALY ratio. It was not clear if the resources were generalisable to other settings.
Analysis and results:
The model structure was well reported, with a diagram. The authors reported a number of limitations to their study, including the lack of evidence on long-term survival with trastuzumab, the omission of other therapeutic regimens, and the reliance on non-Chinese studies of patients with gastric cancer. The authors stated that their study was the first economic evaluation of trastuzumab in patients with advanced gastric cancer, and they discussed the budgetary circumstances in the Chinese health system. It was not clear whether a systematic review was necessary to identify the evidence for the model, but it was clear that the limited evidence was the main limitation of the analysis.

Concluding remarks:
Despite some limitations, such as the lack of available data to inform some estimates and hence high levels of uncertainty, the methods of the study were appropriate and comprehensive. The conclusion reached by the authors is a reasonable reflection of the analysis undertaken.

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