Bevacizumab in combination with paclitaxel for HER-2 negative metastatic breast cancer: an economic evaluation

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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 assessed the cost-effectiveness of bevacizumab in combination with paclitaxel as chemotherapy for patients with human epidermal growth factor receptor 2-negative, metastatic breast cancer. The authors concluded that bevacizumab in addition to paclitaxel was not cost-effective, but further research was needed as there were limited data available from one clinical trial. The methods seem to have been appropriate and the results were clearly and transparently reported. The conclusions reached by the authors appear to be appropriate.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective was to assess the cost-effectiveness of chemotherapy using bevacizumab in combination with paclitaxel for patients with human epidermal growth factor receptor 2-negative metastatic breast cancer.

Interventions
Bevacizumab plus paclitaxel was compared with paclitaxel alone as primary chemotherapy. All patients received 90mg per m$^2$ of paclitaxel on days one, eight, and 15 of a 28-day cycle. The intervention group also received 10mg per kg of bevacizumab on days one and 15.

Location/setting
Switzerland/out-patient care.

Methods
Analytical approach:
A Markov model was used to synthesise the published data from various sources, including a key randomised controlled trial. The study population was a hypothetical cohort of Swiss women with an average height of 1.64m and body weight of 65kg. The analysis was over a patient’s lifetime and the authors stated that the perspective was that of the Swiss health care system.

Effectiveness data:
The effectiveness data were primarily from a clinical trial entitled the E2100 study (Miller, et al. 2007, see ‘Other Publications of Related Interest’ below for bibliographic details). The clinical data for the efficacy of bevacizumab included progression-free survival and overall survival. Major adverse events, such as hypertension, infections, and cerebrovascular ischaemia, were included.

Monetary benefit and utility valuations:
The preference-based utility values were from a Canadian published study that used the time trade-off technique (Leung, et al. 1999, see ‘Other Publications of Related Interest’ below for bibliographic details) and data collected in the E2100 study.

Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs). These benefits were not discounted due to the short life expectancy of the population.
Cost data:
The direct medical costs were included for medications, laboratory tests, management of disease progression, and adverse events. The resource use was based on patient-level data from the E2100 study and another study. The unit costs were from Swiss national drug prices and tariffs. All costs were reported in 2008 Euros (EUR) and an exchange rate of 1.62 Swiss francs equals EUR 1.00 was applied, where necessary. The costs were not discounted due to the short life expectancy of the patients.

Analysis of uncertainty:
The uncertainty was measured in one-way sensitivity analyses on the key parameters. No confidence intervals were available for most of the parameters, so the base-case values were varied by ±30%. The median time to progression and the median time from progression to death were varied by ±50%. Probabilistic sensitivity analyses, using second-order Monte Carlo simulations, were undertaken, with triangular distributions for all parameters. Scenario analyses were performed to assess subgroups by age; patients with different body weights; an assumption of equal time to progression in both arms; and a reduction in the dosage of bevacizumab while assuming the same efficacy. The results were expressed in cost-effectiveness scatter plots and tornado diagrams.

Results
In the base-case for all ages, the mean undiscounted cost per patient was EUR 69,042 for bevacizumab plus paclitaxel and EUR 28,673 for paclitaxel alone; an incremental cost of EUR 40,369 with bevacizumab. Bevacizumab plus paclitaxel was associated with mean undiscounted QALYs of 0.90 compared with 0.69 for paclitaxel alone. The gain in QALYs was 0.21 with bevacizumab.

The incremental cost per QALY gained for bevacizumab plus paclitaxel compared with paclitaxel alone was EUR 189,427 and by age group it ranged from EUR 152,894 in 27- to 49-year-olds to EUR 1,226,615 in 65- to 85-year-olds.

The univariate analysis found that the factors having the strongest impact on the results were progression-free survival and post-progression survival. There was zero probability that the incremental cost per QALY was under the willingness-to-pay threshold of EUR 60,000. The scenario analyses found that lowering the dosage of bevacizumab from 10 to 2.5mg per kg could produce an incremental cost per QALY below this threshold.

Authors’ conclusions
The authors concluded that bevacizumab in addition to paclitaxel was not cost-effective, but further studies were needed as there were limited data available and one clinical trial primarily contributed to this conclusion.

CRD commentary
Interventions:
The interventions were adequately described and the authors gave clear dosage information. The comparators appear to have been appropriate. Bevacizumab might be authorised for use and an appropriate option in other settings.

Effectiveness/benefits:
The effectiveness data were from a study with a good design. The authors did not report a systematic review to identify the available evidence for the model, which makes it unclear whether all the best available evidence was used. The utility values were measured directly from a sample of Canadian patients and from those in the E2100 study; these studies should be consulted to assess their methods and quality. The life expectancy for most of these patients was less than one year and so it was appropriate that no discounting was undertaken.

Costs:
The perspective was that of the Swiss health care system and all the relevant direct medical resources appear to have been analysed, including those for several important adverse events. The resource quantities, the unit costs, and the monthly costs were reported separately and fully referenced. The costs were appropriately adjusted for inflation and no discounting appears to have been appropriate.

Analysis and results:
The analytic approach was satisfactorily reported and the results were reported clearly. The authors acknowledged a
number of limitations to their study including: the reliance on data from a single clinical trial, where the results could differ from real practice; the omission, as comparators, of other combination therapies, which had trial results forthcoming; and the number of missing quality-of-life estimates from the E2100 study. They evaluated the impact of variation in these data, in thorough sensitivity and scenario analyses, and presented all the results. Steps were taken to validate the model, using checking and calibration techniques.

**Concluding remarks:**

*The methods seem to have been appropriate and the results were clearly and transparently reported. The conclusions reached by the authors appear to be appropriate.*

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