Cost-effectiveness of HER2 testing and trastuzumab therapy for metastatic breast 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 assessed the cost-effectiveness of human epidermal growth factor receptor-2 protein testing and subsequent trastuzumab treatment in combination with chemotherapy, compared with chemotherapy alone for metastatic breast cancer patients. The most cost-effective strategies were trastuzumab and chemotherapy for patients with immunohistochemical test 2+ and 3+ results, which were confirmed with fluorescence in situ hybridisation (FISH), and for all FISH test positive patients. The study was based on robust methodology, and the authors’ conclusions appear to be valid.

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

Study objective
The objective was to assess the cost-effectiveness of human epidermal growth factor receptor-2 protein (HER2) testing and subsequent trastuzumab treatment in combination with chemotherapy, compared with chemotherapy alone for metastatic breast cancer (MBC) patients with tumours that overexpress HER2.

Interventions
The five strategies were: chemotherapy alone for all patients; trastuzumab for patients whose immunohistochemical (IHC) test score was 3+; trastuzumab for patients with IHC scores of 2+ and 3+; trastuzumab for patients with IHC 2+ and 3+ scores, which were confirmed with fluorescence in situ hybridisation (FISH); and trastuzumab for all patients with a positive FISH test. Trastuzumab was administered at a 4mg/kg loading dose followed by 2mg/kg every week.

Location/setting
Sweden/hospital.

Methods
Analytical approach:
This economic evaluation used a Markov model which was developed to evaluate the cost-effectiveness of the five strategies. A lifetime horizon was considered and the authors stated that a societal perspective was adopted.

Effectiveness data:
The clinical data were derived from a selection of known studies. The treatment effect and MBC progression were derived from a recent published clinical trial which compared trastuzumab plus docetaxel with docetaxel alone. All cause mortality was derived from Swedish life tables. The details of the study used to obtain the test accuracy were not given. The primary clinical outcomes were time to progression, and overall survival.

Monetary benefit and utility valuations:
The utility valuations were derived from a published study that estimated the Health Related Quality of Life in different breast cancer stages from Swedish breast cancer patients.

Measure of benefit:
Quality-adjusted life-years (QALYs) were used as the summary benefit measure, and were estimated using the decision model. The life-years (LYs) gained were also reported. It is not clear whether discounting was applied.

Cost data:
The categories of costs were drugs (trastuzumab and docetaxel, including outpatient services and monitoring), tests (IHC and FISH), outpatient visits, inpatient services, treatment of adverse events associated with trastuzumab, and palliative care. The costs of informal care were included but costs associated with productivity losses were not considered due to the advanced age of the patient population. The drug costs were derived from the Swedish pharmaceutical reference book, with dosages reflecting actual treatment patterns. Other costs were based on experts’ opinions, a naturalistic study, and other published sources, the details of which were not given. The costs of tests were derived from an official price list of a large university hospital. All costs were in Swedish kronor (SEK) and the price year was 2005.

Analysis of uncertainty:
Alternative scenarios were considered for the assumptions about inpatient and outpatient costs and utility valuations. A deterministic univariate sensitivity analysis was also undertaken by varying key model inputs by 30%. A two-way sensitivity analysis was performed on the impact of changes in the sensitivity and specificity of the IHC test. Furthermore, a probabilistic sensitivity analysis was completed.

**Results**
The expected QALYs gained were 1.280 with chemotherapy alone, 1.408 with trastuzumab for IHC 3+ patients, 1.456 with trastuzumab for IHC 2+ and 3+ patients, 1.456 with trastuzumab for IHC 2+ and 3+ patients with FISH confirmation, and 1.471 with trastuzumab for all FISH positive patients.

The expected costs were SEK 331,668 with chemotherapy alone, SEK 395,398 with trastuzumab for IHC 3+ patients, SEK 438,429 with trastuzumab for IHC 2+ and 3+ patients, SEK 416,732 with trastuzumab for IHC 2+ and 3+ patients with FISH confirmation, and SEK 425,174 with trastuzumab for all FISH positive patients.

The incremental analysis revealed that, after excluding dominated strategies, the incremental cost was SEK 485,039 per QALY gained (and SEK 332,252 per LY gained) with trastuzumab for IHC 2+ and 3+ patients with FISH confirmation (over chemotherapy alone), and SEK 561,207 per QALY gained (and SEK 384,427 per LY gained) with trastuzumab for all FISH positive patients (over trastuzumab for IHC 2+ and 3+ patients with FISH confirmation).

The sensitivity analysis showed that the most influential model inputs were utility scores, risk of breast cancer related death, and inpatient or outpatient costs.

**Authors’ conclusions**
The authors concluded that a strategy of giving trastuzumab plus chemotherapy to those patients with FISH confirmation of IHC 2+ and 3+ results, and a strategy of giving trastuzumab plus chemotherapy to all FISH positive patients were both cost-effective for MBC patients with overactive HER2 receptor tumours.

**CRD commentary**
**Interventions:**
The rationale for the selection of the interventions was clear and appropriate given the current treatment patterns in the authors’ setting.

**Effectiveness/benefits:**
The sources of clinical data were selected by the authors. However, the treatment effect and transition probabilities were based on a recent clinical trial which was generally characterised by high internal validity. The authors appropriately included only those patients who did not cross-over between treatment groups in the trial. Few details on the other sources of clinical data were provided. The derivation of the benefit measure was clearly described, especially with respect to the source of quality-of-life adjustments for the calculation of QALYs.

**Costs:**
The analysis of costs was consistent with the perspective adopted in the study. The authors described the cost categories and the assumptions made to derive the data. However, except for some relevant national databases, little information on the sources was given. The price year was appropriately reported. No statistical tests of costs were performed.
Analysis and results:
The synthesis of costs and benefits was appropriately performed and discussed. The issue of uncertainty was extensively addressed in the sensitivity analysis, the main findings of which were clearly presented. The authors compared their findings with those from other studies. Also, a detailed discussion was provided around the implications of using alternative estimates for cost and effectiveness assumptions. The authors acknowledged that the main limitation of the analysis was the generalisability of the economic and clinical data used in the study.

Concluding remarks:
Overall, the study was based on robust methodology, although more details on some clinical sources would have been useful. Nevertheless, the authors’ conclusions appear to be valid.

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