HER-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis


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.

Health technology
The identification of patients with metastatic breast cancer, whose tumours exhibited human epidermal growth factor receptor-2 protein (HER-2) overexpression or gene amplification, and their subsequent treatment with trastuzumab was examined. HER-2 was identified by either an immunohistochemical assay (IHC) kit detecting protein overexpression (HercepTest, HT), or by fluorescence in situ hybridisation (FISH), which detected gene amplification.

Type of intervention
Secondary screening and treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 65-year-old women newly diagnosed with metastatic breast cancer.

Setting
The setting was secondary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1987 and 2003. The costs were derived from sources published between 1997 and 2002. Year 2002 prices were used.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A Markov state-transition model was developed, to evaluate the long-term effectiveness and costs of seven strategies for identifying and treating metastatic breast cancer patients with HER-2 positive tumours. Once on treatment, patients could move to one of four possible health states. The health states possible were complete or partial response to therapy, stable disease, progressive disease, or death. The model was run in weekly cycles. First-line therapy was discontinued on disease progression, and no patient received more than eight cycles of chemotherapy. Chemotherapy consisted of paclitaxel alone. It was assumed that any objective response to therapy (complete or partial reduction of tumours) would occur within 18 weeks of treatment. Trastuzumab was assumed to provide no additional benefit in the absence of HER-2 gene amplification. The patients were expected to receive subsequent treatment regimens after disease progression, but mortality in the progressive disease state did not depend on initial treatment or HER-2 status. Death
due to breast cancer was possible among women with progressive disease, while death resulting from other causes was possible at any state. FISH was assumed to be a 'gold' standard for HER-2 status.

**Outcomes assessed in the review**
The outcomes assessed were the characteristics of HT compared with FISH, and the transition probabilities of the Markov model.

**Study designs and other criteria for inclusion in the review**
It was stated that most of the transition probabilities for the Markov model were derived primarily from a randomised clinical trial (RCT). No further inclusion criteria for the studies were reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Only studies that compared HT with FISH used in accordance with the test manufacturers’ instructions, on a series of unselected cases, and which reported results in adequate detail were included in the analysis.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Approximately 13 primary studies were included in the review.

**Methods of combining primary studies**
The results of individual primary studies were combined in the case of test characteristics for the identification of HER-2 overexpression. The average HT characteristics were calculated with each study's estimate weighted by the respective sample size of FISH+ and FISH-negative (FISH-) cases. Transition probabilities were verified by calibration with the end points of the RCT from which they were derived. The trial was simulated using a first-order Monte Carlo technique. The final transition probabilities used in the economic model were derived from the calibration model.

**Investigation of differences between primary studies**
Potential differences between the primary studies were not discussed further.

**Results of the review**
The probabilities of HT scores conditional on a FISH+ result were 0.079 for 0 and 1+ scores together, 0.250 for 2+ score, and 0.671 for 3+ score.

The probabilities of HT scores conditional on a FISH- result were 0.843 for 0 and 1+ scores together, 0.140 for 2+ score, and 0.017 for 3+ score.

The transition probabilities of the Markov model were as follows:

the objective response rate for HER-2 positive cases was 54% for chemotherapy plus trastuzumab and 27% for chemotherapy alone;
the objective response rate for HER-2 negative cases was 38%;

the monthly probability of disease progression for HER-2 negative cases was 12% in stable disease state and 9% in response state;

the relative increase in progression rate for HER-2 positive cases receiving chemotherapy alone was 1.5%;

the relative reduction in progression rate for HER-2 positive cases due to trastuzumab was 0.8%;

the monthly probability of death as a result of progressive disease was 5%; and

the prevalence of HER-2 positive disease was 25%.

**Measure of benefits used in the economic analysis**

The measure of benefit used was the number of quality-adjusted life-years (QALYs) gained from adopting each of the strategies examined. The utility weights for the base-case analysis were elicited from a sample of US oncology nurses. These utilities incorporated the impact of paclitaxel side effects on quality of life. It was assumed that the utility of each health state was equivalent for patients on chemotherapy plus trastuzumab and those on chemotherapy alone. An overview of breast cancer utility studies provided the utility weights used in the sensitivity analysis. The health benefits were estimated over the patients' lifetime and were discounted at an annual rate of 3%.

**Direct costs**

The direct costs included breast cancer-related medical costs and patient costs. Medical costs comprised the costs of HER-2 tests (HT or FISH), medication (trastuzumab and paclitaxel), premedication for paclitaxel, chemotherapy infusion, monitoring and/or treating side effects, oncologist visits, and treating progressive disease. Patient costs referred to the costs of travel for infusion visits and the time spent in treatment. The quantities and the unit costs were analysed separately for most of the cost elements considered in the analysis.

Some quantities, such as the number of oncologist visits, the travelling distance for infusion visits, and the monitoring tests required before and during treatment with trastuzumab, were based on authors' assumptions. HER-2 testing costs, cost of chemotherapy infusion, costs associated with monitoring and/or treating side effects, and oncologist visit unit costs were valued at their Medicare reimbursement amount. Medication costs were estimated using the Drug Topics Red Book and the Medicare Reimbursement Rates. Medicare relative value units, geographic practice components, and laboratory fees were obtained from the 2002 National Physician Fee Schedule and the 2002 Clinical Laboratory Fee Schedule. The costs of treating chemotherapy side effects and of treating progressive disease were derived from studies published in 1997 to 1998. The unit costs of travel were based on the standard mileage rate for calculating tax-deductible business travel. Patient time was valued using average annual earnings data collected in the Current Population Survey, 2002. Estimates of the quantity of time spent in treatment were not provided.

The total costs were derived using modelling. All the costs were expressed in 2002 values. Discounting was carried out at an annual rate of 3%, as the costs were incurred during the lifetime of the patients.

**Statistical analysis of costs**

The costs were treated deterministically. No statistical analysis of the costs was undertaken.

**Indirect Costs**

The indirect costs associated with the overall course of disease were not included in the analysis.

**Currency**

US dollars ($).
Sensitivity analysis
A sensitivity analysis was undertaken to test the impact of variability in the parameter values on the results. All input parameters of the model were assessed in one- and two-way sensitivity analyses. The ranges for HT characteristics were derived from 95% confidence intervals of the weighted average values used in the base-case scenario. The ranges for the rest of the input parameters were derived from published literature and assumptions.

Estimated benefits used in the economic analysis
The QALYs gained per patient with each of the strategies were:

- no initial test and chemotherapy alone for all patients, 1.28 QALYs;
- HT alone and additional trastuzumab for HT 3+, 1.34 QALYs;
- HT alone and additional trastuzumab for HT 2+ and 3+, 1.36 QALYs;
- HT followed by FISH for HT 2+ and 3+ and additional trastuzumab for FISH+, 1.36 QALYs;
- HT followed by FISH for HT 2+ and additional trastuzumab for HT 3+ and FISH+, 1.36 QALYs;
- FISH alone and additional trastuzumab for FISH+, 1.37 QALYs; and
- no initial test and additional trastuzumab for all patients, 1.37 QALYs.

Cost results
The total costs per patient associated with each of the strategies were:

- no initial test and chemotherapy alone for all patients, $43,314;
- HT alone and additional trastuzumab for HT 3+, $51,231;
- HT alone and additional trastuzumab for HT 2+ and 3+, $57,467;
- HT followed by FISH for HT 2+ and 3+ and additional trastuzumab for FISH+, $53,702;
- HT followed by FISH for HT 2+ and additional trastuzumab for HT 3+ and FISH+, $54,056;
- FISH alone and additional trastuzumab for FISH+, $54,738; and
- no initial test and additional trastuzumab for all patients, $79,181.

Synthesis of costs and benefits
The costs and benefits were combined in the form of incremental cost-effectiveness ratios (ICERs). The following strategies were dominated and excluded from further analysis:

- HT alone and additional trastuzumab for HT 3+;
- HT followed by FISH for HT 2+ and additional trastuzumab for HT 3+ and FISH+;
- HT alone and additional trastuzumab for HT 2+ and 3+; and
- no initial test and additional trastuzumab for all patients.

Only two strategies were not ruled out by simple or extended dominance. Compared with no initial test and chemotherapy alone for all patients, HT followed by FISH for HT 2+ and 3+ and additional trastuzumab for FISH+ had
an ICER of $125,100/QALY gained. Compared with the latter strategy, FISH alone and additional trastuzumab for FISH+ had an ICER of $145,400/QALY gained.

In the sensitivity analysis, with the exception of changes in test characteristics, wide variations in the parameter values had little impact on the results. The magnitude of ICERs was affected slightly, but the rank order of strategies did not change, nor did the presence of simple and extended dominance. The cost-effectiveness ranking of strategies changed only when the diagnostic characteristics of HT varied.

In order to explore the effect of test characteristics on the outcomes, HT was replaced by a hypothetical IHC, the results of which were categorised as positive or negative. The testing strategies evaluated were no test, IHC alone, IHC with FISH confirmation of positive results (IHC+FISH), and FISH alone. Trastuzumab was given to patients found HER-2 positive. Two-way sensitivity analyses were undertaken. With an IHC specificity of 100%, the ICER of IHC compared with no test and chemotherapy alone was approximately $124,000/QALY as IHC sensitivity varied between 50 and 100%. The ICER of FISH alone increased from $129,000/QALY when IHC sensitivity was 50%, to more than $450,000/QALY when IHC sensitivity was 99%. At all values of IHC specificity, FISH alone was dominated if IHC sensitivity was 100%. IHC+FISH dominated IHC alone if IHC specificity was less than 99.6%, regardless of its sensitivity. Below this specificity threshold, the ICER of IHC+FISH remained relatively constant for varying values of IHC sensitivity. When IHC specificity was 60% and sensitivity was less than 70%, IHC+FISH was ruled out by extended dominance.

Authors’ conclusions
It was more cost-effective to use fluorescence in situ hybridisation (FISH) alone or as confirmation of all positive HercepTest (HT) results, rather than using FISH to confirm only weakly positive results or using HT alone. The test characteristics had a substantial impact on the aggregate costs and effectiveness of treatment.

CRD COMMENTARY - Selection of comparators
Several strategies related to the identification and treatment of HER-2 positive patients with metastatic breast cancer with trastuzumab were discussed. HT and/or FISH testing represented alternative methods for the identification of patients eligible for trastuzumab treatment, and were licensed in the USA for this purpose. You should consider whether any of these interventions reflects widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The authors did not report that a systematic review of the literature had been undertaken to identify all relevant research and minimise biases. They also did not report the sources searched to identify relevant research. Possible sources of information were identified, and the data were combined where necessary using appropriate methods (such as weighted averages) to estimate the parameters necessary for the model. Potential differences between the primary studies were not discussed any further. Uncertainty was evaluated in the model using a sensitivity analysis based on all the outcomes derived from the literature.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The Markov model used for this purpose was appropriate since it enabled the estimation of the long-term benefits obtained by the adoption of each strategy. All future benefits were discounted at a rate of 3% per annum. The utility values were not derived from patients’ preferences, as recommended for a reference-case cost-effectiveness analysis, but from US oncology nurses. The authors stated that such estimates were not available for the health states in their model.

Validity of estimate of costs
Although it was implicitly stated that the study adopted a societal perspective, productivity losses over the course of the disease were not included in the analysis. The costs and the quantities were reported separately for the majority of cost elements included in the analysis, which enables the results to be reproduced. The cost estimates were derived from
published studies and other sources, and sensitivity analyses were conducted using appropriate ranges. Discounting was appropriately undertaken since the costs were incurred during the patients’ lifetime. The date to which the prices referred was reported, which improves the generalisability of the results.

**Other issues**
The authors did not compare their findings with those of other studies. The issue of the generalisability of the results to other settings was not addressed. The results of the analysis were presented in full. The authors reported a number of limitations to their study. For example, the assumptions that FISH was the gold standard for identifying HER-2 amplification, that the response rates used in the model were independent of the HT result (depending only on the FISH result), and that single-gene copy HER-2 overexpressers did not benefit from trastuzumab. An additional limitation highlighted was that recent technological and policy developments (e.g. computerised image analysis, quantitative interpretation of IHC assays), which might alter the HER-2 testing debate, were not considered in the analysis. The authors’ conclusions reflected the scope of the analysis.

**Implications of the study**
The authors suggested that a policy of undertaking IHC with FISH confirmation of all positive results would only be preferable to FISH alone if the willingness to pay for a one-year gain in quality-adjusted survival was in the narrow range of $125,000 to $145,000. Otherwise, if treatment with trastuzumab was considered to be worth the cost, then the authors felt that initial testing with FISH should be worth the cost as well. However, they stated that technological and policy developments in HER-2 testing may affect both the costs and accuracy of IHC and FISH and, in this case, a reanalysis of the cost-effectiveness of alternative testing strategies would be required.

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