Cost-effectiveness of letrozole versus tamoxifen as initial adjuvant therapy in hormone receptor-positive postmenopausal women with early-stage 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.

Health technology
The study examined 5-year adjuvant therapy with letrozole, a third-generation aromatase inhibitor, in postmenopausal women with hormone receptor (HR)-positive early breast cancer (BC). Letrozole was compared with tamoxifen as first-line adjuvant treatment for women who had completed primary surgical therapy.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis and cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of postmenopausal women with HR-positive early BC who had completed primary surgical therapy. The mean age of the typical patient was 60 years.

Setting
The setting was an outpatient clinic. The economic study was carried out in the USA.

Dates to which data relate
The clinical data were derived from studies published between 1983 and 2006. No dates for the resource consumption data were explicitly reported. The price year was 2005.

Source of effectiveness data
The clinical data used in the model were:

the probabilities of first BC events (contralateral tumour, locoregional recurrence, distant metastases and BC death) with letrozole and tamoxifen;

the transition probabilities among health states;

the probabilities of adverse events (endometrial cancer, venous thromboembolism, myocardial infarction, unstable angina, heart failure, hip fracture, other fractures, arthralgia and hypercholesterolaemia) with letrozole and tamoxifen; and

the death rates in different groups of patients (women without distant metastases or adverse events, women with distant metastases and women with adverse events).
Modelling
A Markov model with a lifetime horizon (30 years) and annual cycles was used to simulate the clinical and economic impact of the two treatments in a hypothetical cohort of patients. The model was adapted from a previous decision model in a similar patient population. The model included health states that were defined on the basis of disease stage. A schematic representation of the model was given, together with a description of transition patterns. The health states, which were reported, represented typical cancer progression. A key model assumption was the carry-over effect of letrozole, the benefits of which were assumed to last for 5 years after treatment discontinuation.

Sources searched to identify primary studies
The probabilities of first BC events over the first 5 years for both letrozole and tamoxifen were derived from the Breast International Group (BIG) 1-98, an ongoing multinational, randomised double-blinded trial of tamoxifen versus letrozole. The probabilities of first BC in years 5 to 15 data were obtained from the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis of tamoxifen. Other studies were also used to determine transition probabilities, although they were not described. The probabilities of adverse events came from the BIG 1-98 study, the Surveillance Epidemiology and End Results programme (SEER), published data from the Rochester Epidemiology Project (REP), data from the Marshfield Epidemiology Study, data for patients presenting to Duke University Medical Center between 1986 and 1997, and the National Surgical Adjuvant Breast and Bowel Project (a large multi-centre, randomised placebo-controlled trial). Death rates were obtained from age-specific annual mortality rates for American women (for women without metastases or adverse events), the Letrozole P025 trial (for women with distant cancer), SEER and REP publications, and a prospective study of 7,500 women (for women with adverse events).

Methods used to judge relevance and validity, and for extracting data
No systematic search for data was reported, thus the primary studies might have been identified selectively. However, data for the long-term effect of tamoxifen were obtained from a meta-analysis, while data for letrozole were taken from a large, randomised controlled trial.

Measure of benefits used in the economic analysis
The summary benefit measures used were the expected number of life-years (LYs) and quality-adjusted life-years (QALYs) associated with the two treatments. QALYs were modelled and calculated by combining data on survival and utility weights. The latter values were derived mainly from a sample of 44 American women who had early-stage BC, and were elicited using a chained standard-gamble technique. Assumptions were also made when determining the utility weights associated with non-hip fractures. The utility decrements for cardiac adverse events were derived from a longitudinal cohort study of health status in a community setting. The benefits were discounted at an annual rate of 3%.

Direct costs
The analysis was performed from the perspective of the health care system. It included the costs associated with adjuvant hormonal therapy, BC events (health states) and the treatment of adverse events. The unit costs were not presented separately from the quantities of resources used. The costs of adjuvant therapy were estimated using wholesale acquisition prices. The costs of BC events were derived from a large Midwestern health care system (charges were adjusted using a cost-to-charge multiplier). The costs of adverse events came from published studies. The sources of the resource use data were not explicitly stated but some data were derived from published studies. Discounting was relevant, as the costs were incurred over a long timeframe, and an annual rate of 3% was applied. The price year was 2005.

Statistical analysis of costs
The costs were treated deterministically in the base-case analysis.

Indirect Costs
Productivity costs were not considered.

**Currency**  
US dollars ($).

**Sensitivity analysis**  
The issue of uncertainty was addressed by performing both a deterministic and a probabilistic sensitivity analysis. In the former, key clinical and economic inputs of the model were varied across their published confidence intervals (CIs) or from 50 to 150% of the base-case values. Alternative scenarios considered patients initiating therapy at age 50 and 70 years, model timeframes of 20 and 40 years, and discount rates of 0% and 5%. The probabilistic sensitivity analysis assigned stochastic distributions to model inputs and generated cost-effectiveness acceptability curves.

**Estimated benefits used in the economic analysis**  
The discounted LYs were 13.71 (undiscounted 18.41) with tamoxifen and 14.15 (undiscounted 19.09) with letrozole. The difference was 0.44 LYs (undiscounted 0.68).

The discounted QALYs were 12.73 (undiscounted 16.99) with tamoxifen and 13.14 (undiscounted 17.62) with letrozole. The difference was 0.41 QALYs (undiscounted 0.63).

**Cost results**  
The total costs per patient were $75,665 with tamoxifen and $85,370 with letrozole (difference $9,705). This difference was mainly due to higher therapy costs and higher costs associated with cardiac events for letrozole, despite the reduction in costs associated with BC care.

**Synthesis of costs and benefits**  
Incremental cost-effectiveness ratios and cost-utility ratios were calculated in order to combine the costs and benefits of the two strategies.

The incremental cost per LY gained with letrozole over tamoxifen was $22,209. The incremental cost per QALY gained with letrozole over tamoxifen was $23,743.

The sensitivity analysis produced some interesting results. For example, the cost-effectiveness of letrozole was sensitive to the relative risk of BC events for letrozole compared with tamoxifen, with the incremental cost per QALY ranging from $15,623 to $52,959 over the CI of this clinical parameter. The results of the analysis were also sensitive to age at initiation of therapy ($16,606 per QALY gained for women aged 50 years and $108,638 per QALY gained for women aged 70 years). In addition, when no carry-over effect for letrozole was assumed, the cost per QALY gained rose to $39,098.

Variations in other model inputs did not substantially alter the results of the base-case analysis since the incremental cost per QALY gained with letrozole remained below the commonly cited threshold of $50,000 per QALY.

The probabilistic sensitivity analysis suggested that the 95% CI for the cost-utility ratio was $14,087 to $51,129. Letrozole was the preferred strategy in 97% of simulations at a willingness-to-pay of $50,000 per QALY, and in 99% of simulations at a willingness-to-pay of $75,000.

**Authors’ conclusions**  
From the perspective of the US health care system, letrozole used as adjuvant treatment for postmenopausal women with hormone receptor (HR)-positive early breast cancer (BC) was a cost-effective alternative to tamoxifen. The analysis suggested that treatment might be more cost-effective in younger patients (those starting therapy at 50 years
of age).

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparators was clear in that tamoxifen represented the conventional treatment for postmenopausal women with HR-positive early BC, while letrozole was one of the most recent aromatase inhibitors available on the market. The authors did not include anastrozole in their comparison, stating that there was considerable uncertainty in cost-effectiveness analyses comparing letrozole with anastrozole. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from published studies. Such studies might have been identified selectively as the authors did not report the methods and conduct of a systematic review of the literature. However, extensive information on the primary studies in terms of design and patient population was provided. In addition, most of the primary sources used to determine treatment effect were clinical trials or meta-analyses, which usually represent valid sources of clinical data. Some assumptions about the duration of treatment effect were made and the impact of these assumptions was investigated in the sensitivity analysis.

Validity of estimate of measure of benefit
The estimation of health benefits (LYs and QALYs) was modelled using the Markov model. The utility weights were taken from published sources, which were described together with the instrument used. Both discounted and undiscounted results were presented. The use of an alternative discount rate (or no discounting) was investigated. Both benefits are comparable with the benefits of other health care interventions. QALYs are an appropriate benefit measure as they capture the impact of the treatments on two relevant dimensions of health for women with BC (i.e. survival and quality of life).

Validity of estimate of costs
The analysis of the costs was consistent with the authors' stated perspective. It was restricted to the analysis of direct medical costs. A detailed breakdown of the cost items was not provided and the costs were mainly presented as macro-categories. Little information on resource use was given, which might limit the possibility of replicating the analysis in other settings. The cost calculation was modelled using the Markov framework. Statistical analyses of the costs were performed only in the probabilistic sensitivity analysis. However, uncertainty surrounding key cost estimates was investigated in the deterministic sensitivity analysis. The price year was reported, which will assist with reflation exercises in other time periods.

Other issues
The authors reported the results from other cost-effectiveness analyses of aromatase inhibitors and found them to be similar to findings in the literature. The issue of the generalisability of the study results to other settings was only implicitly addressed in the sensitivity analyses. However, the use of a probabilistic sensitivity analysis will have enhanced the external validity of the study. The authors presented their results in full and provided a cost-effectiveness plane and a cost-effectiveness acceptability curve. Some limitations of the analysis were also noted. For example, the authors acknowledged that some clinical estimates (i.e. incidence of adverse events) were derived from published studies that might not be generalisable to postmenopausal women with early BC. Although the sensitivity analysis showed that the base-case results were not sensitive to these and other estimates such as costs of adverse events, the authors stated that caution will be required when interpreting this aspect of the analysis.

Implications of the study
The study results suggest that adjuvant therapy with letrozole should be used for postmenopausal women with HR-positive early BC.

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