Cost utility analysis of first-line hormonal therapy in advanced breast cancer: comparison of two aromatase inhibitors to tamoxifen

Dranitsaris G, Verma S, Trudeau M

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 use of hormonal agents, the aromatase inhibitors letrozole and anastrozole, as first-line treatment of hormone-sensitive breast cancer in postmenopausal women.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The target population was postmenopausal women with hormone-sensitive advanced breast cancer.

Setting
The setting was secondary care. The economic analysis was carried out in Canada.

Dates to which data relate
The effectiveness data related to 2000 and 2001 for the hormonal agents, and from 1983 to 2000 for the other treatments considered in the decision model. The resource use data related to 2000. The price year was 2003.

Source of effectiveness data
The effectiveness data for the hormonal agents were derived from a meta-analysis of randomised trials from 1990 onwards.

Modelling
A decision tree was used to estimate the costs and utilities of letrozole and anastrozole as first-line therapies in the treatment of advanced hormone-sensitive breast cancer. Chemotherapy was assumed to be the second-line therapy for nonresponders to hormonal agents. This was followed by palliative care for patients who failed to respond to chemotherapy. The patients were assumed to receive 3 months of hormone therapy, after which the responders remained on therapy until disease progression while the nonresponders (those patients with disease progression at 3 months) received 3 cycles of chemotherapy. After 3 cycles of chemotherapy, the nonresponders were given palliative care and the responders received 3 further cycles of chemotherapy.

Outcomes assessed in the review
The outcomes assessed in the review were progression-free survival, the rates of response to hormonal therapy and the
side effect rates. These were assessed for letrozole, anastrozole and tamoxifen.

**Study designs and other criteria for inclusion in the review**
The review considered only randomised trials published in peer-reviewed journals. The inclusion criteria specified that the trial participants were postmenopausal women with either positive or unknown oestrogen or progesterone receptor status, who had not received tamoxifen before as first-line therapy for advanced stage cancer. In addition, one treatment arm of each trial had to consist of either 2.5 mg/day letrozole, 1 mg/day anastrozole or 20 mg/day tamoxifen. The authors stated that similar criteria were used to select studies of the second-line therapies considered in the decision model.

**Sources searched to identify primary studies**
MEDLINE, Cancerlit and the Cochrane Library were searched for randomised trials.

**Criteria used to ensure the validity of primary studies**
Not stated.

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

**Number of primary studies included**
Six primary studies of hormonal agents were included in the review.

**Methods of combining primary studies**
The results from the studies were pooled using a random-effects meta-analysis.

**Investigation of differences between primary studies**
The authors do not appear to have investigated differences between the primary studies. This was relevant as the pooled meta-analysis of response rates was based on single treatment arms from randomised trials. By taking the absolute rather than the relative response rates, the benefits of randomisation are lost and the pooling of response rates between different trials may be inappropriate.

**Results of the review**
The calculated pooled response rates were 29.0% (95% confidence interval, CI: 25 - 33) for anastrozole, 30.0% (95% CI: 26 - 35) for letrozole and 24.2% (95% CI: 18.6 - 29.7) for tamoxifen.

The median progression-free survival was 255 days for anastrozole, 287 days for letrozole and 214 days for tamoxifen.

**Measure of benefits used in the economic analysis**
The measure of benefits used in the economic analysis was the quality-adjusted progression-free years. The utility scores were derived from a published study and were assessed using the time trade-off method. In this study, the utility assessments were obtained from a random sample of 25 Canadian women living in Ontario, Canada. The utilities obtained related to treatment with anastrozole or letrozole, and for the purposes of the study the authors assumed that the utility associated with tamoxifen was the same. The utility values were estimated to be 0.45 for no response to first-line therapy and progression during chemotherapy, 0.67 for no response to first-line therapy but response to chemotherapy, and 0.80 for response to first-line therapy.
Direct costs
The costs and the resource quantities were not reported separately. The study included the costs to the Canadian health care system. These were for hormonal agents, hospitalisation, outpatient visits, antiemetics, chemotherapy, laboratory tests, patient monitoring and the treatment of adverse effects, and related physician visits. The costs were obtained from pharmacy ordering catalogues and the Departments of Biochemistry, Microbiology and Diagnostic Imaging at Princess Margaret Hospital in 2001. The costs were derived primarily from a published study, and were entered into the decision model. The study reported the average costs estimated for each treatment in the decision model. The authors did not specify the method used to adjust for inflation. They also did not report the duration of the decision model, so it was not possible to relate the average cost per patient to the duration of treatment. The requirement for discounting was unclear.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not include, which was consistent with the perspective of the study.

Currency
Canadian dollars (Can$). The conversion to US dollars was Can$1 = US$0.6 at the price year used in the study (1 April 2003).

Sensitivity analysis
Several one-way sensitivity analyses were performed. These were used to investigate the generalisability of the results to patients who receive different kinds of chemotherapy as second-line treatment. Also, to investigate the uncertainty in response rates and costs of chemotherapy. In the base-case analysis, the patients were assumed to have standard chemotherapy consisting of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). The sensitivity analyses explored the use of single-agent paclitaxel or docetaxel for patients who had already received an anthracycline-based regimen in the adjuvant setting. The response rates for anastrozole and letrozole were varied to the upper and lower bounds of the CIs from the meta-analysis. The cost per cycle of each of the chemotherapy regimens was varied to the upper and lower bounds of the CI from the published cost study.

Estimated benefits used in the economic analysis
Tamoxifen was associated with an estimated 0.44 quality-adjusted progression-free years per patient, letrozole with 0.49 and anastrozole with 0.47. The authors did not state the duration of the model, so it is not possible to ascertain the duration of benefits or the need for discounting. The study considered withdrawals from treatment due to adverse events and drug toxicity.

Cost results
The average costs (reported in 2003 prices) were $2,847 per patient for anastrozole, $2,883 per patient for letrozole and $2,258 per patient for tamoxifen. The costs of adverse events were reported to have been included in the analysis, but the authors stated in their conclusions that the costs of drug-related side effects were not included. Thus, only the adverse effects of the second-line therapy were considered. The duration of treatment was unclear from the study.

Synthesis of costs and benefits
The average cost-utility ratios were derived by combining the costs and benefits to produce a cost per quality-adjusted progression-free year. This was $5,100 for tamoxifen, $5,900 for letrozole and $6,100 for anastrozole. The incremental cost per quality-adjusted progression-free year gained was $12,500 with letrozole (relative to tamoxifen) and $19,600 with anastrozole (relative to tamoxifen). The study only considered the cost-effectiveness of the new agents relative to...
tamoxifen, rather than comparing all three alternatives to ascertain the most cost-effective of the three. The authors justified this by asserting that there was no head-to-head trial of letrozole and anastrozole.

The authors reported a threshold of $20,000 for determining the cost-effectiveness. The incremental cost per quality-adjusted progression-free year gained with letrozole, compared to tamoxifen, did not exceed $20,000 in the sensitivity analyses. However, the corresponding incremental cost per quality-adjusted progression-free year gained with anastrozole did exceed $20,000 when the response rate to anastrozole was at the lower bound of the CI, and when the cost of FAC chemotherapy was at the lower bound of its CI. The authors concluded that the sensitivity analyses demonstrated that letrozole is the preferred treatment option in terms of cost-effectiveness.

**Authors’ conclusions**

While both anastrozole and letrozole are cost-effective alternatives to tamoxifen, letrozole should be the treatment of choice.

**CRD COMMENTARY - Selection of comparators**

Tamoxifen was chosen as the comparator since it was current practice in the study setting. You should consider whether tamoxifen represents current first-line therapy in your own setting.

**Validity of estimate of measure of effectiveness**

The authors reported the review method used to obtain the primary studies, including the sources and inclusion criteria. However, they did not state that a systematic review of the literature had been undertaken. The estimates of effectiveness were combined using a random-effects meta-analysis. The authors do not appear to have investigated the validity of the meta-analysis by investigating differences between the primary studies or publication bias. The authors appear to have pooled absolute response rates rather than relative treatment effects, thus heterogeneity between the trials could be important.

**Validity of estimate of measure of benefit**

The estimation of benefits was modelled. The decision tree was a suitable model for this estimation, but the generalisability of the results was hindered by the authors’ failure to report the duration of the decision model. The use of quality-adjusted progression-free years rather than life-years allowed the authors to make use of time to disease progression reported in the clinical trials.

**Validity of estimate of costs**

The study considered a wide range of costs relevant to the perspective adopted. The authors acknowledged that the cost of treating drug-related side effects was omitted and that this is likely to have biased the model toward tamoxifen, which is associated with a higher incidence of thromboembolic events. The costs and the quantities were not reported separately, and were derived from a published study.

A sensitivity analysis of the chemotherapy costs was undertaken. The prices were obtained from the authors' setting and were treated deterministically. The prices used were charges and this reflects the perspective adopted. The generalisability of the cost data was affected by the authors’ failure to report the duration of the decision model.

**Other issues**

The authors did not compare the findings of their study with similar cost-utility analyses. The issue of the generalisability to other settings was not addressed. The authors did not present their results selectively and their conclusions reflected the scope of the analysis. The authors reported that their study was limited by a lack of head-to-head comparisons between letrozole and anastrozole. They also acknowledged that their model did not consider second-line hormonal therapy as an alternative to chemotherapy. However, in their defence, they stated that the crossover data suggested that the response rates to each of the drugs as second-line therapies were comparable.
Implications of the study
The authors recommended that letrozole be the first-line therapy for hormone-sensitive advanced breast cancer in postmenopausal women in Canada.

Source of funding
Supported by Novartis, Canada.

Bibliographic details

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Agents, Hormonal /economics /therapeutic use; Aromatase /antagonists & inhibitors; Breast Neoplasms /drug therapy /economics; Canada; Comparative Study; Cost-Benefit Analysis; Decision Support Techniques; Enzyme Inhibitors /economics /therapeutic use; Humans; Meta-Analysis; Nitriles /economics /therapeutic use; Quality of Life; Research Support, Non-U.S. Gov’t; Tamoxifen /economics /therapeutic use; Triazoles /economics /therapeutic use

AccessionNumber
22003000947

Date bibliographic record published
31/05/2004

Date abstract record published
31/05/2004