Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive 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 use of anastrozole (1 mg) as initial adjuvant therapy for women with early-stage estrogen receptor-positive breast cancer.

Type of intervention
Treatment.

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

Study population
The study population comprised a hypothetical cohort of women with early-stage estrogen receptor-positive breast cancer. The inclusion criteria specified postmenopausal women with operable breast cancer who had undergone primary surgery and/or completed chemotherapy.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1997 and 2003. No explicit dates for the resource use data were provided. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and assumptions (based on expert opinion).

Modelling
A Markov model was constructed to determine the natural history of the disease in two hypothetical cohorts of women (those receiving anastrozole and those receiving tamoxifen). The typical patient was a 64-year-old woman with early-stage estrogen receptor-positive breast cancer. Women entered the model in the state "well while receiving adjuvant therapy" and could then experience vaginal bleeding or venous thromboembolism (VTE), hip fracture, local recurrence or contralateral breast cancer, or systemic breast cancer recurrence. Adjuvant therapy was halted after 5 years, or if an adverse event occurred earlier. The patients could also die of cancer-related or other causes. The timeframes examined in the model ranged from 4 years (corresponding to the current length of follow-up in the ATAC trial) to 20 years (corresponding to the average life expectancy of a 64-year-old woman in the USA). Annual cycles were considered. The duration of adjuvant therapy was 5 years.
Outcomes assessed in the review
The outcomes derived from the literature were:

- the rates of local recurrence, new contralateral breast cancer, and systemic recurrence, and the median time from systemic recurrence to death;
- the relative risks (RRs) associated with anastrozole use, such as new contralateral breast cancer, local recurrence, systemic recurrence resulting in death, and death due to other causes;
- the treatment-associated RR ratios for hip fracture, vaginal bleeding, VTE, and death following hip fracture; and
- the annual treatment-associated event probabilities for hip fracture, vaginal bleeding, and VTE.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature had been undertaken. The design of the primary studies was generally not reported. The exception was the ATAC trial, which was satisfactorily described.

Sources searched to identify primary studies
There was no suggestion that any sources were searched.

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
Eleven primary studies were provided the evidence.

Methods of combining primary studies
Most data were taken from a primary study.

Investigation of differences between primary studies
Not stated.

Results of the review
The annual rate of local recurrence was 0.8%.

The annual rate of new contralateral breast cancer was 0.3%.

The annual rate of systemic recurrence was 1.8%.

The median time from systemic recurrence to death was 21 months (range: 12 - 36).

The RRs associated with anastrozole use were 0.56 (range: 0.32 - 0.98) for new contralateral breast cancer, 0.78 (range: 0.54 - 1.14) for local recurrence, 0.835 (range: 0.66 - 1.05) for systemic recurrence, and 1 for systemic recurrence resulting in death.
The RR for death due to other causes was age-dependent and was not reported.

The treatment-associated RR ratios for hip fracture were 1.6 (range: 1.3 - 2) overall, 0.77 (range: 0.67 - 0.87) for tamoxifen, and 1.23 (range: 1.13 - 1.34) for anastrozole.

The other treatment-associated RR ratios were 0.54 (range: 0.4 - 0.8) for vaginal bleeding with anastrozole, 0.59 (range: 0.5 - 1) for VTE with anastrozole, and 1.5 (range: 1 - 3) for death (all causes) following hip fracture.

The annual probabilities of hip fracture were 0.13% for age 64-67 years, 0.27% for age 67-70 years, 0.54% for age 71-75 years, 1% for age 76-80 years, 1.8% for age 81-85 years, and 3.1% for age 86-90 years.

The 30-day mortality following hip fracture was 15% (range: 0 - 50).

The rate of vaginal bleeding in the tamoxifen cohort was 2.9%, hysterectomy was required in 25% (range: 0 - 50) of patients, and the 30-day mortality following vaginal bleeding was 0% (range: 0 - 1).

The rate of VTE in the tamoxifen cohort was 1.3% (range: 1 - 2) and the 30-day mortality following VTE was 2% (range: 0 - 5).

Methods used to derive estimates of effectiveness
Some assumptions based on author’s and experts’ opinions were made.

Estimates of effectiveness and key assumptions
The utility penalties used in the model were:

- 15 days (range: 0 - 60) for local breast recurrence,
- 45 days (range: 0 - 90) for contralateral breast cancer,
- 0.7 (range: 0.5 - 1) for systemic recurrence and hip fracture,
- 15 days (range: 0 - 45) for vaginal bleeding, and
- 30 days (range: 0 - 90) for VTE.

If an adverse event did not occur, the relative benefits of anastrozole were assumed to persist indefinitely. After any form of breast cancer recurrence, all benefits associated with reductions in the incidence of other forms of breast recurrence were lost, and the type of treatment received and survival were the same in both arms. Vaginal bleeding and VTE could each occur only once and could not occur beyond 5.5 years from the start of therapy. The projected difference in hip fracture risk was due in equal part to a reduction in risk in the tamoxifen arm and an increase in risk in the anastrozole arm.

Measure of benefits used in the economic analysis
The three summary benefit measures used were DFS, projected survival, and quality-adjusted life-years (QALYs). DFS was defined as freedom from contralateral breast cancer, local recurrence, systemic recurrence, or death due to any cause. All three measures were all derived from the decision model: An annual discount rate of 3% was applied because of the long timeframe of the analysis. Utility weights were derived from experts’ opinions.

Direct costs
The costs were discounted at an annual rate of 3% because they were incurred over a long time horizon. The unit costs were not presented separately from the quantities of resources used, and some costs were presented as macro-categories. The health services included in the economic evaluation were tamoxifen, anastrozole, and the treatment of
disease and adverse events. The cost/resource boundary of the third-party payer was adopted. Treatment patterns were based on author's opinions. The costs were derived from Medicare payments and the acquisition costs of drugs. Although the price year for all costs was not clearly stated in the paper, the author has informed us that it was 2004.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate sensitivity analyses were performed to determine the robustness of the cost-effectiveness and cost-utility ratios to variations in key model inputs. The model inputs investigated included anastrozole-induced reduction in the RR of systemic recurrence, the additional cost of anastrozole, the RR of non breast cancer-related death, the RR of systemic recurrence, survival with metastases, and the RR and quality of life of hip fracture. The ranges used were generally derived from published data.

**Estimated benefits used in the economic analysis**
The increase in DFS with anastrozole in comparison with tamoxifen was 1.8% at 4 years, 3.4% at 8 years, 4.1% at 12 years, and 3.4% at 20 years.

The increase in overall survival with anastrozole in comparison with tamoxifen was 0.4% (median 2 days) at 4 years, 1.1% (median 11 days) at 8 years, 1.6% (median 26 days) at 12 years, and 1.8% (median 60 days) at 20 years.

The median increase in quality-adjusted survival with anastrozole in comparison with tamoxifen was 4 days at 4 years, 14 days at 8 years, 26 days at 12 years, and 45 days at 20 years.

**Cost results**
The total costs per patient associated with the two treatments were not reported.

**Synthesis of costs and benefits**
Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of the two alternative adjunctive therapies.

The incremental cost per year of DFS gained with anastrozole in comparison with tamoxifen was $167,500 at 4 years, $60,700 at 8 years, $32,800 at 12 years, and $16,700 at 20 years.

The incremental cost per life-year gained with anastrozole in comparison with tamoxifen was $1,112,000 at 4 years, $235,400 at 8 years, $96,000 at 12 years, and $40,600 at 20 years.

The incremental cost per QALY gained with anastrozole in comparison with tamoxifen was $533,000 at 4 years, $201,800 at 8 years, $111,300 at 12 years, and $75,900 at 20 years.

The sensitivity analysis showed that the results of the model were highly sensitive to the cost of anastrozole, the RR of systemic breast cancer recurrence, and quality of life associated with hip fractures. For example, an increase of $1 in the price of anastrozole would increase the incremental cost-effectiveness ratio by approximately $5,000 per year of
DFS, $9,200 per life-year, and $12,000 per QALY. Similar variations were found for the RR of systemic breast cancer recurrence and quality of life associated with hip fractures.

Authors’ conclusions
When the timeframe of the analysis was limited to 4 years (corresponding to the trial follow-up period), anastrozole resulted in a modest benefit at a high cost in comparison with tamoxifen for women with early-stage estrogen receptor-positive breast cancer. However, when a long-term perspective was taken, the projected benefits were substantial and anastrozole represented a cost-effective strategy in comparison with tamoxifen. With a time horizon exceeding 12 years, the cost-effectiveness of anastrozole was below the threshold of $50,000 to $100,000 per life-year or quality-adjusted life-year (QALY) gained.

CRD COMMENTARY - Selection of comparators
The selection of tamoxifen as the comparator was appropriate since it represented the prototype and first known anti-estrogen agent used to treat breast cancer. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published source. Most of the clinical data were derived from a well-conducted clinical trial, which was double-blinded and adequately powered to detect statistically significant differences in the clinical end points. Details of the other primary studies were not reported. It would appear that the primary studies were identified selectively and a review of the literature was not undertaken. The methods used to extract and combine the primary estimates were not reported. Some assumptions were also made. The issue of uncertainty was addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
All three summary benefit measures were appropriate and detected the impact of the interventions on patient health. Some assumptions were made to derive the utility weights used in the calculation of QALYs. Survival and QALYs are easily compared with the benefits of other health care interventions. Discounting was applied, as recommended in US guidelines. The impact of variations in the discount rate was not investigated.

Validity of estimate of costs
The author stated explicitly the perspective that was adopted in the study. All relevant categories of costs were included in the analysis. There was limited information on some items as some costs were presented as macro-categories. This limits the possibility of replicating the study since a detailed breakdown of the costs was not provided. The source of the costs was given, but resource use was mainly derived from author's opinions. Such data were not varied in the sensitivity analysis. The price year was not reported, which makes reflaction exercises in other settings difficult. The costs were treated deterministically and only the additional cost of anastrozole was changed in the sensitivity analysis.

Other issues
The author did not compare the findings of this study with those from other studies. However, he has since informed us that, at the time of this study there were no other comparable publications. The issue of the generalisability of the study results to other settings was not explicitly addressed. However, sensitivity analyses were carried out and these increased the external validity of the analysis. The study referred to women with early-stage estrogen receptor-positive breast cancer and this was reflected in the author's conclusions.

Implications of the study
The author suggested that better results could be achieved in women whose risk of hip fracture was lower than that observed in the trial. Therefore, the study results supported recommendations suggesting that bone mineral density should be measured before the initiation of hormonal therapy.
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