Cost-effectiveness of anastrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced 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
Postmenopausal women with predominantly hormone receptor-positive advanced breast cancer were given anastrozole (1 mg/day) as first-line therapy. The comparator was tamoxifen (20 mg/day).

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost-utility analysis.

Study population
Postmenopausal women with predominantly hormone receptor-positive advanced breast cancer who were receiving first-line therapy were eligible for inclusion in the trial, subject to several clinical criteria. The full details of the inclusion criteria were given in the original effectiveness paper. Patients with tumours known to be estrogen and/or progesterone receptor-negative were excluded from the study, as were those who were estimated to have a survival of less than 3 months. At the beginning of the study patients receiving bisphosphonates were excluded. However, after 270 patients had been recruited, this condition was relaxed as so many women were being treated with bisphosphonates.

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

Dates to which data relate
For the effectiveness evidence, the patients were recruited between 1996 and 1998. The final date of the evidence was not given, but it must have been before February 2000 (when the original effectiveness paper was submitted). The resource evidence corresponded to the same dates as the effectiveness evidence. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a single study (Nabholtz et al., see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was carried out prospectively using the same patients who provided the effectiveness data.

Study sample
There was no mention of a sample size being planned before the trial and it was unclear how the patients were selected. In total, 353 postmenopausal women with predominantly hormone receptor-positive advanced breast cancer were
randomised to either anastrozole with tamoxifen placebo (n=171), or tamoxifen with anastrozole placebo (n=182). The numbers of women who refused to participate or were excluded from the original sample were not reported.

**Study design**
This was a randomised, double-blind, multi-centred controlled trial. The randomisation scheme was stratified by centre, but the method of randomisation was not stated. Follow-up was until objective progression or death. There was no mention of any loss to follow-up.

**Analysis of effectiveness**
The basis of the analysis was intention to treat until disease progression. Disease progression was defined as the presence of at least the appearance of any new lesion, an increase of at least 25% in the sum of existing measured lesions (compared to the most favourable previous assessment), or a worsening of non-measurable disease. If the patient died before disease progression, the date of death was substituted for the date of disease progression.

The patients were followed up every 6 months until death. The health outcome assessed for the two kinds of treatment was progression-free survival time (TTP). The incidence, severity and duration of 15 different adverse events were recorded. These were the expected side effects of the medication. They ranged from gastrointestinal disturbance, weight gain, and depression, to venous thromboembolism.

The comparability of the two groups was described in the original effectiveness paper, in which detailed clinical information and demographic characteristics were given. The authors stated that the two groups were well balanced according to these characteristics, but did not give statistical results. In the concluding discussion, the authors stated that there were more visceral liver metastases in the tamoxifen group (16.5%) than in the anastrozole group (7.6%). Hormone receptor status was positive in 151 (out of 171) of the anastrozole group and 162 (out of 182) of the tamoxifen group.

**Effectiveness results**
The median TTP was 11.1 months for the anastrozole group and 5.6 months for the tamoxifen group, (p=0.005). The median QATTP was 8.8 months for the anastrozole group and 4.6 months for the tamoxifen group, (p=0.002).

The incidence of adverse events was different in the two patients groups, but the difference was not analysed statistically. Lethargy, vaginal bleeding, venous thromboembolism, coronary thrombosis and thromboembolic disease were more common in the tamoxifen group, whereas hot flushes and vaginal dryness were more common in the anastrozole group.

Nine patients in the anastrozole group withdrew from the study because of adverse events, of which 3 were thought to be drug related. Eight patients in the tamoxifen group withdrew from the study, of which 5 were thought to be drug related.

**Clinical conclusions**
The authors concluded that, for postmenopausal women with advanced breast cancer, anastrozole offers better outcomes than tamoxifen for first-line therapy. This advantage holds when the side effects of the treatment are taken into consideration.

**Modelling**
A Cox proportional hazards model was used to estimate the median quality-adjusted time to disease progression (QATTP). A Kaplan-Meier model was used in the original effectiveness paper to estimate the TTP and in the current paper to estimate the QATTP. A 2-stage model using probit and tobit regressions was used to estimate the incremental cost difference per patient after disease progression to death between the two treatment arms. This compensated for the
fact that not all the patients had died or experienced disease progression at the time of the analysis.

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

The measure of benefit, quality-adjusted progression-free survival time (QATTP), was defined as the time without any toxicity or disease progression. The time with toxicity was discounted to be less valuable than toxicity-free time. Two different measures of QATTP were calculated. One considered all adverse events as equally undesirable. The other gave utility weights of 0.7 for mild toxicity, 0.5 for moderate toxicity and 0.3 for severe toxicity. All these “utility” values were assumed. QATTP was calculated by applying the Q-TWIST method (Glasziou et al., see Other Publications of Related Interest) to the effectiveness measure, TTP. A Cox proportional hazards model was used to estimate the median QATTP.

**Direct costs**

The hospital costs were included in the analysis. The costs measured were for drug acquisition, drug-related adverse events, inpatient hospital costs, outpatient hospital costs, surgery, radiotherapy, other hormonal therapies, chemotherapy, and all other medications.

The quantity of resource use was measured at the same time as the effectiveness evidence. Resource use associated with adverse events was taken from a different effectiveness study, as it was not available for the current study (Bonnettre J et al., see Other Publications of Related Interest). The price of the daily drug dose of tamoxifen and anastrozole was taken from a published source. The costs of drug therapy after disease progression were also taken from a published source. The costs for non-pharmaceutical health care resources were taken from a cost analysis of managed care administrative claims data, which showed a cost that varied according to the kind of health insurance plan.

Discounting was not relevant since the costs were during less than two years. The price year was 2000.

**Statistical analysis of costs**

No statistical analysis of the costs was carried out.

**Indirect Costs**

No indirect costs were calculated.

**Currency**

US dollars ($).

**Sensitivity analysis**

The authors examined the sensitivity of the results to variation in the price of tamoxifen, and to the type of weighting of toxicities.

**Estimated benefits used in the economic analysis**

The median QATTP without sensitivity grading for toxicities was 8.8 months for the anastrozole group and 4.6 months for the tamoxifen group. The risk ratio was 1.49 (95% confidence interval, CI: 1.20 - 1.84; p=0.002).

The median QATTP with sensitivity grading was 9.7 months for the anastrozole group and 4.6 months for the tamoxifen group. The risk ratio was 1.47 (95% CI: 1.19 - 1.81; p=0.003).

The median increase in QATTP was 4.2 months for anastrozole without adjusting for the severity of the side effect, and 5.1 months when such an adjustment was made.
The patients were followed up until death. At the time of the initial effectiveness study, 28.3% of the patients had died and the median duration of follow-up was 18 months.

**Cost results**
The authors used a method of cost calculation that resulted in cost variation according to the type of health insurer. The mean treatment cost for patients treated with tamoxifen was $28,521 for indemnity, $37,189 for PPO, $34,301 for POS, and $27,495 for HMO.

For patients treated with anastrozole, the mean cost was $18,843 for indemnity, $22,917 for PPO, $21,587 for POS, and $18,431 for HMO. The p-value for the difference in costs was p<0.01.

The costs of adverse events were included.

The cost reduction resulting from anastrozole was $9,678 for indemnity, $14,273 for PPO, $12,715 for POS, and $9,064 for HMO.

**Synthesis of costs and benefits**
The costs and benefits were not combined. Anastrozole was found to be the dominant strategy as it saved costs. Even when the authors varied the price of tamoxifen to zero there was still a cost-saving associated with anastrozole. Both methods of calculating the QATTP showed anastrozole to be superior to tamoxifen. This improvement increased when the severity of side effects was considered.

**Authors' conclusions**
Anastrozole was superior to tamoxifen in its impact on quality-adjusted time to disease progression (QATTP). It also caused a reduction in the total medical costs incurred per patient.

**CRD COMMENTARY - Selection of comparators**
The selection of tamoxifen as the comparator was justified by it being the preferred first-line treatment for postmenopausal women with breast cancer who have hormone-sensitive disease. However, there may well be other relevant comparators and these should be considered.

**Validity of estimate of measure of effectiveness**
The effectiveness data were derived from a single study based on a randomised controlled trial, which was appropriate for the hypothesis. The authors did not report how many women were excluded from the randomisation process or how the patients were selected. Therefore, it is uncertain how representative they were of postmenopausal women with predominantly hormone receptor-positive advanced breast cancer. The authors reported that the study sample had a higher level of visceral metastases (48%) than in other studies (35%). The patients groups were not shown to be comparable using statistical means, but they appear to have been similar except for the higher level of liver metastases in the tamoxifen group. Apart from the lack of information on the patients initially excluded, the analysis of effectiveness was handled credibly.

**Validity of estimate of measure of benefit**
The estimation of benefit, QATTP using two different methods of evaluating side effects, was based on assumed utility weights for toxicity. Consequently, the authors undertook sensitivity analyses to test whether the results changed when the weights were related to severity. This was appropriate and it did not change the results significantly.

**Validity of estimate of costs**
The authors adopted a cost perspective of a health insurance company, which would not be generalisable to other health
systems such as the National Health Service. They did not explain the factors that caused the cost differences between the insurance systems. All the relevant costs were included in the analysis, although the indirect costs were not. Their inclusion would probably have strengthened the authors' conclusion that tamoxifen was a more expensive treatment when all costs are considered. The costs were not broken down into prices and quantities, although the unit cost of certain non pharmaceutical resources was given according to each kind of health insurance system.

The resource use quantities were generally taken from a single study. The exception was those associated with adverse events, which were taken from a published source. The authors carried out a sensitivity analysis in which all the costs in the tamoxifen group after disease progression were reduced by 33%, yet the tamoxifen patients still incurred higher costs than the anastrozole patients. A statistical analysis of the prices was not carried out, but a sensitivity analysis on the price of tamoxifen was. When the price of tamoxifen was set to zero the anastrozole patients still incurred lower costs, although the authors did not report the exact figures. The price year was 2000.

**Other issues**
The authors made appropriate comparisons of their results with the findings of other studies. However, they did not address the issue of generalisability. This was a disadvantage as it means that the cost analysis will be of much less interest to a non-US audience. The authors could have presented more complete results on women excluded from the trial. It would also have been useful had they broken down the costs into prices and quantities. They could also have explained the differences in costs according to the type of insurer, and shown which came closest to a societal cost. In the original study, the authors noted the higher rate of visceral metastases in the study as compared with other studies.

**Implications of the study**
The implications of the study are that, for postmenopausal women with advanced hormone receptor-positive breast cancer, anastrozole offers superior first-line therapy to tamoxifen. It provided better QATTP and also resulted in lower costs, even if tamoxifen was priced at zero.

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**Other publications of related interest**


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