Cost effectiveness of letrozole in the treatment of advanced breast cancer in postmenopausal women in the UK

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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
Letrozole in the treatment of advanced breast cancer in postmenopausal women in the United Kingdom (UK).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The analysis involved a hypothetical cohort of patients who were identical to patients recruited from a clinical trial. The women were postmenopausal, had positive or unknown estrogen and/or progesterone receptors and were not experiencing rapidly progressive disease. They had also experienced a relapse on adjuvant anti-estrogen therapy or within a year after ceasing adjuvant anti-estrogen therapy that was given for more than 6 months or had progressed from first-line anti-estrogen therapy for advanced disease.

Setting
The setting of the study was the UK National Health Service (NHS) and the economic study was carried out in the UK.

Dates to which data relate
A collection of studies was used to generate the model, the effectiveness and resource use information for which was collected from studies dated between 1985-1997. 1996 price data were used.

Source of effectiveness data
The estimate for final outcomes was based on a review of the literature and on opinion.

Modelling
A semi-Markov model was used in order to combine the costs and effectiveness of the treatments associated with the second-line management of advanced breast cancer in postmenopausal women.

Outcomes assessed in the review
For second-line hormone treatment the outcomes assessed in the review were the probabilities for:

1) disease progression without serious adverse events;
(2) disease progression with serious adverse events;

(3) no disease progression without serious adverse events; and

(4) no disease progression with serious adverse events.

For third-line hormone, chemotherapy 1 and chemotherapy 2 treatment, the outcomes assessed were the probabilities for disease progression and mortality.

**Study designs and other criteria for inclusion in the review**

Data for the second-line hormone treatment were derived from a double-blind, randomised, multi-centred trial (AR/BC2). For the third-line hormone, chemotherapy 1 and 2 treatments a collection of trials were used. Study inclusion criteria were provided.

**Sources searched to identify primary studies**

Not stated.

**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**

The main data source for second-line hormone treatment was a randomised, double-blind clinical trial. The different probabilities relating to the efficacy and mortality of third-line hormone therapy was based on three studies: a multi-centre randomised trial, a small one-centre trial, and a retrospective study. The different probabilities of the efficacy and mortality of the first chemotherapeutic regimen were based on 8 studies: 4 randomised studies, a non-blind prospective study, 2 retrospective analyses, and a review of 9 randomised studies. The different probabilities on the efficacy and mortality of the second chemotherapeutic regimen were based on 3 studies: a non-blind prospective study, a retrospective analysis (n=32) and a review of 85 clinical studies.

**Methods of combining primary studies**

Results from the studies used in the analysis were combined by the narrative method.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

The results of the review were as follows:

The authors state that the clinical trial results for letrozole show a clear advantage in terms of time to progression and duration of disease.

No letrozole patients were reported to experience treatment-related serious adverse events compared to 12.2% of megestrol patients.

60.6% of letrozole patients had no progression after 3 months compared to 58.2% of megestrol patients.
17.8% of letrozole patients had no treatment failure after 1.5 years compared to 6.9% of megestrol patients.

The time to death was 25.3 months for letrozole patients compared to 21.5 months for megestrol patients.

For 55% of the patients on third-line hormone therapy, remission of disease, either an objective response or stabilisation, was achieved with a median duration of 7.3 months. The median survival time was 16 months.

83% of the patients receiving a first chemotherapy regimen achieved a remission, the median duration of which was 6.9 months and the median survival time 14.5 months.

61% of patients receiving a second chemotherapy regimen achieved a remission, the median duration of which was 4.8 months and the median survival time 9.1 months.

Methods used to derive estimates of effectiveness
The probabilities for therapeutic choices and the units of healthcare utilisation were derived from expert opinion, as were the probabilities for disease progression and mortality. A modified Delphi technique was used to make adjustments to reflect local treatment patterns in the UK.

Estimates of effectiveness and key assumptions
Most effectiveness information was collected from the AR/BC2 trial and published literature, while expert opinion was used for the health care utilisation data.

Measure of benefits used in the economic analysis
Life years gained was the outcome measure used in the economic analysis. A semi-Markov model was used in order to estimate the costs and effectiveness associated with the second-line management of advanced breast cancer in postmenopausal women, and the published literature was used to populate the model.

Direct costs
Costs were discounted at a rate of 5%. Quantities were reported separately from costs. For all resources, costs were derived from the Birmingham City Hospital. A combination of in-depth real costs and costs estimated to the hospital’s best ability were combined to generate costs. The direct medical costs included drug therapy, consultations and the number of days of hospitalisation. Data sources included the clinical trial of letrozole, the literature, official price and tariff lists and expert opinion. NHS charges for acute admissions were used for in-patient health care utilisation and health care utilisation of serious adverse events. The charge of nursing care was based on an estimation of time spent by a specialist oncology nurse. 1997 market prices for letrozole and megestrol were used but costs were reported for 1996.

Statistical analysis of costs
Not undertaken.

Indirect Costs
Not included.

Currency
UK pounds sterling (£)

Sensitivity analysis
Sensitivity analyses were performed on the main probabilities and cost assumptions to observe the robustness of
findings to a range of values that the variables could take. A number of one-way sensitivity analyses were undertaken as well as analysis of extremes.

**Estimated benefits used in the economic analysis**
The analysis covered treatment initiation until death. The effectiveness outcomes, average survival time and time without progression, favour letrozole. The average survival time of the letrozole group was 2.1 years (25.2 months) versus 1.9 years (22.8 months) for the megestrol group, that is a gain in survival of 2.4 months (10.5%). The average time without progression, cumulatively calculated over the different treatment options, amounted to 20.2 months for letrozole and 17.8 months for megestrol, an increase of 13.7% for the former patients.

**Cost results**
The total average cost per patient for the treatment of advanced breast cancer starting from second-line hormone therapy until death was 7,547 for the letrozole group and 6,820 for the megestrol group. The higher costs incurred by the letrozole group were mainly due to costs for second-line hormone therapy, which had higher acquisition costs and longer duration of response to letrozole. The main cost driver was hospitalisation (45% of total costs).

**Synthesis of costs and benefits**
The incremental cost-effectiveness of letrozole per life-year gained was 3,588. The cost per month without progression gained with letrozole over megestrol was 299. The findings were not sensitive to changes in costs of hospitalisation, chemotherapy and serious adverse events with regard to the incremental cost effectiveness. The minimum and maximum estimates of the experts were used as a range for those variables with the largest variation. This resulted in a range of incremental cost-effectiveness ratios varying from 3,239 - 4,137. The model was highly sensitive to the acquisition costs of letrozole and megestrol, and to the efficacy and safety parameters with second-line hormone therapy.

**Authors' conclusions**
The authors conclude that, under the assumptions used in their Markov model, letrozole represents a cost-effective treatment for the NHS compared to standard care. They suggest that further studies, particularly prospective head-to-head comparisons, are required before determining the superiority of one type of therapy over another.

**CRD COMMENTARY - Selection of comparators**
The reason for the choice of comparator is clear.

**Validity of estimate of measure of benefit**
The estimate of the measure of benefit used in the economic analysis is likely to be internally valid.

**Validity of estimate of costs**
Resource quantities were reported separately from prices and adequate details of cost estimation were given. The authors state that there is no guarantee the expert panel's assessment of resource utilisation is an accurate reflection of healthcare delivery in the UK.

**Other issues**
As the authors indicate, the probabilities of clinical events were primarily derived from clinical trials and, as clinical trials have a low external validity, the probabilities for clinical events may not be typical for usual practice. Given the uncertainties in the data the authors' conclusions were justified.
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