Cost-effectiveness analysis of exemestane compared with megestrol in patients with advanced breast carcinoma

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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 exemestane (EXE), compared with megestrol acetate (MA), for the treatment of patients with advanced breast carcinoma. EXE is a new steroidal, irreversible aromatase inactivator.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women with postmenopausal, tamoxifen-refractory advanced breast carcinoma.

Setting
The setting was a hospital. The economic analysis was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were collected from a published study (see Other Publications of Related Interest). The dates during which the cost data were obtained were not reported. The price year was not reported.

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

Link between effectiveness and cost data
The costing was carried out retrospectively after the effectiveness results were known, using the same sample as that used in the effectiveness study.

Study sample
There were 769 women enrolled on the study. The study sample comprised women with advanced breast carcinoma who had failed to respond to tamoxifen treatment, either as adjuvant therapy or as first-line therapy for metastatic disease. The patients were randomised to EXE (n=366) or MA (n=403). The median age was 65 years. Of the enrolled women, about 66% had received prior hormonal therapy for an advanced breast carcinoma, and about 33% of them had an unknown oestrogen receptor status. The Eastern Cooperative Oncology Group performance status distribution was found to be 45% at level 0, 45% at level 1, and 10% at level 2.
The two cohorts had a greater tumour burden than other recent studies as shown by the following characteristics: 57 to 59% of the women had visceral disease, only 31% had bone or skin only involvement, and approximately 80% had measurable disease. A sample size of 750 patients was adequate for testing the hypothesis of equivalence between the treatments in the objective response rate, with a power of 80% (alpha 0.10; one-sided).

**Study design**
The study was a multicentre, international, double-blind, Phase III, randomised controlled trial. The data were examined independently for those patients with responsive disease and blinded to treatment.

**Analysis of effectiveness**
The analysis was performed on an intention to treat basis. The primary health outcomes were:

- the objective response rates;
- the duration of response;
- the time to disease progression;
- the time to treatment failure;
- survival; and
- the quality of life, as measured by the QLQ C-30 questionnaire (European Organisation for Research and Treatment of Cancer).

The patients' characteristics were similar to those participating in other trials for this condition. All the characteristics were balanced between treatment groups.

**Effectiveness results**
The median time to tumour progression was significantly longer in the EXE cohort (20.3 weeks) than in the MA cohort (16.6 weeks), (p=0.037).

There were no differences in the aggregate global health score between the groups, prior to disease progression.

There were few Grade 3 or 4 adverse events in either group. Adverse drug events led to the discontinuation of therapy in 1.7% of the EXE patients and in 5.0% of the MA patients.

The EXE cohort had a greater percentage survival at both 1 and 2 years after randomisation, compared with the MA cohort. At 1 year, the survival rates were 82% for the EXE group and 75% for the MA group. At 2 years, the survival rates were 60% for the EXE group and 54% for the MA group.

The authors made several assumptions. First, the costs, quality of life, and survival after the development of progressive disease were independent of initial therapy. Secondly, the distribution of the events or risks in the two cohorts had the same shape and variance.

**Clinical conclusions**
Compared with MA, EXE was projected to increase the survival of the patients.

**Modelling**
The median survival of patients who received EXE was projected from a Cox model using a 1,000-day timeframe. This was necessary as the median survival of patients receiving EXE was not achieved.
Measure of benefits used in the economic analysis
The measure of health benefits used was the number of life-years gained. The health benefits were discounted at an annual rate of 3%.

Direct costs
The direct costs were discounted at an annual rate of 3%. The quantities and costs were reported separately. The direct costs related to the cost of the drugs. The quantity/cost boundary adopted was that of a society. The drug costs were derived from the current average wholesale price. The price year was not reported.

Statistical analysis of costs
The authors reported 95% confidence intervals (CIs) for the drug costs per patient.

Indirect Costs
The indirect costs were discounted at an annual rate of 3%. The quantities and costs were reported separately. The indirect costs related to the additional health care expenses, and lost wages for the family or companion. The quantity/cost boundary adopted was that of a society. The price year was not reported.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were conducted on the costs, discount rate, and efficacy estimates.

Estimated benefits used in the economic analysis
The daily hazard rate for death was 0.0008 for MA, and ranged from 0.000472 to 0.000792 for EXE.

The average survival at 1,000 days was 688 days for MA, and ranged from 690.4 to 797 days for EXE.

The survival rate at 1,000 days was 44.8% for MA, and ranged from 45.2 to 62.3% for EXE.

The median survival was 123.4 weeks for MA and 160.3 weeks for EXE.

The average survival at 1,000 days using a 3% discount rate was 631.4 days for MA and 684.9 days for EXE. The incremental benefit was equivalent to 53.5 days.

Cost results
The average total drug costs per patient amounted to $235 (95% CI: 221 - 324) for MA and $1,517 (95% CI: 1,204 - 1,847) for EXE. Using a 3% discount rate, the average treatment costs amounted to $231 for MA and $1,490 for EXE.

Synthesis of costs and benefits
The incremental cost per life-year saved with EXE, over MA, was $10,600 (95% CI: 6,200 - 209,000). The sensitivity analysis showed that the cost-effectiveness ratio was much more sensitive to changes in the efficacy projections than the cost projections.

Authors' conclusions
The potential risks and costs of exemestane (EXE) were low for postmenopausal women with hormonally responsive breast carcinoma, who failed to respond to chemotherapy with tamoxifen. For these patients, EXE (25 mg daily) had minimal risks and may provide substantial benefits at a very modest cost.

**CRD COMMENTARY - Selection of comparators**
The comparator used was justified on the grounds that it represented a commonly used strategy. You should decide if these health technologies are relevant to your setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on a randomised controlled trial, which was appropriate for the study question. The study sample was representative of the study population, although the authors noted that the study groups had a greater tumour burden than those patients enrolled in other recent studies. The analysis of effectiveness was handled credibly. The reader should be aware that, given that the median survival had not been reached in the EXE study, the authors had to base their survival estimates on projections.

**Validity of estimate of measure of benefit**
The benefits were estimated directly from the effectiveness analysis. Death may not have been the ideal primary end point of the analysis, given the modest number of adverse events.

**Validity of estimate of costs**
There were several positive aspects of the cost analysis. First, all the relevant direct and indirect cost categories were included. Secondly, the quantities and costs were reported separately. Thirdly, statistical and sensitivity analyses were conducted on the costs. However, there were also several limitations. The price year was not reported, which would make reflation exercises in other settings more difficult. Also, more information about the source of the indirect cost estimates could have been provided. Since the drug costs were estimated from the average wholesale prices, the true opportunity costs were also not estimated. Finally, the authors did not consider the protocol-specific costs due to radiological imaging and laboratory tests.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies but did not address the issue of generalisability to other settings. In addition, they did not compare other treatment alternatives such as anastrozole and letrozole. The authors did not appear to present their results selectively. The study considered postmenopausal women with hormonally responsive breast carcinoma who failed to respond to chemotherapy with tamoxifen, and this was reflected in the authors’ conclusions.

The authors made several assumptions. First, the costs, quality of life, and survival after the development of progressive disease were independent of initial therapy. Secondly, the distribution of events or risks in the two cohorts had the same shape and variance. No justification for these assumptions was provided.

The reader should note the wide CIs for the cost-effectiveness. These ranged from well within most decision-makers’ thresholds to well above. The authors also utilised one source of effectiveness data that was sponsored by the manufacturer, although this fact cannot be taken to imply selection bias.

**Implications of the study**
The potential risks and costs of EXE (25 mg daily) were low for postmenopausal women with hormonally responsive breast carcinoma, who failed to respond to chemotherapy with tamoxifen. For these patients, EXE had minimal risks and may provide substantial benefits at a very modest cost. A direct comparative trial between steroidal and non-steroidal inhibitors to determine the optimal agent would be valuable.
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Other publications of related interest

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