Modeling for cost-effective-adjuvant aromatase inhibitor strategies for postmenopausal women with breast cancer
Younis T, Rayson D, Dewar R, Skedgel C

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 study examined adjuvant upfront aromatase inhibitor (AI) compared with sequential tamoxifen (TAM) and AI for postmenopausal women with breast cancer.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 60-year-old postmenopausal women with hormone receptor-positive breast cancer undergoing adjuvant hormonal therapy. In addition, four hypothetical cohorts with variable 10-year risks of cancer recurrence in the absence of adjuvant systemic therapy were examined. These were defined as follows.

Low risk: node-negative disease with an approximate 25% projected disease relative risk at 10 years.

Average risk: mixed cohort of node-negative (60%) and node-positive (40%) disease with an aggregate estimated risk of disease recurrence of 35%.

High risk: estimated 50% risk of recurrence for node-positive disease.

Very high risk: node-positive patients with a high nodal burden and an approximate 75% risk of disease recurrence.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1998 and 2006. The costs were derived from studies published between 2000 and 2005. The price year was 2005.

Source of effectiveness data
The clinical and epidemiological data used in the model were event rates for cancer recurrence, death with or without recurrence, and adverse events. Event rates for cancer recurrence were derived to reflect estimated 10-year relative risks without adjuvant systemic therapy. Event rates for adverse events were only included in the sensitivity analysis.
Modelling
A Markov state transition model was developed to simulate hypothetical cohorts with variable 10-year risks of cancer recurrence. The Markov model included five health states. Specifically, well on therapy, well off therapy, local relapse, distant relapse, and dead (with or without relapse). Ten- and 20-year horizons were adopted for the model. The duration of each cycle was one month. The model was based on various assumptions concerning efficacy, transition probabilities and costs, which were all reported in the study. However, they are too numerous to be reported here.

Sources searched to identify primary studies
Event rates for cancer recurrence, death and adverse events were derived from the literature and the relevant AI trials. Event rates for adverse events were derived from the Arimidex, Tamoxifen, Alone or in Combination study and the Intergroup Exemestane Study.

Methods used to judge relevance and validity, and for extracting data
The authors reported that data used in the model were derived from the literature. However, the methods used for the review of the literature were not reported. It was also unclear how the results from different studies were combined.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs) gained. Utilities associated with each health state in the model were derived from the literature and ranged from 0 (death) to 1 (perfect health). Since the benefits could be incurred over a 10- or 20-year period, discounting was relevant and was appropriately performed at an annual rate of 3%.

Direct costs
The direct costs to the health care payer were used in the analysis. These comprised the costs of adjuvant hormonal therapy, breast cancer follow-up and cancer recurrence management. The costs of adverse events were accounted for only in the sensitivity analysis. The costs of drugs were based on acquisition costs which, in turn, were based on average wholesale prices in Nova Scotia, Canada. Other costs were derived from the literature. Since the costs could be incurred over a 10- or 20-year period, discounting was relevant and was appropriately performed at an annual rate of 3%. All costs were appropriately adjusted for inflation, and were reported in 2005 prices. The authors did not report the results of their costing study.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The productivity costs were not included.

Currency
Canadian dollars (CAD).

Sensitivity analysis
A series of two-way sensitivity analyses was generated in order to predict cost-effective strategies across a wide range of efficacy hazard ratios. Two-way sensitivity analysis graphs were then generated to illustrate the cost-effective strategy for every combination of hazard rates on the basis of a threshold of $50,000/QALY gained. In addition, different scenarios were examined by varying parameter estimates including hormone receptor expression profile (ER+/PR+ versus ER+/PR-), adverse events perspective, age (+/- 10 years), time horizon (20 versus 10 years), cost-effectiveness threshold (CAD 75,000 versus CAD 50,000/QALY gained), duration of carryover benefit for AI (3
versus 5 years), utility estimates (+/- 10%) and downstream costs (+/- 25%).

**Estimated benefits used in the economic analysis**
The estimated benefits used in the economic analysis were not reported.

**Cost results**
The cost results were not reported.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per QALY gained). The authors did not report the numerical findings of their analysis. They simply reported which intervention was cost-effective at a threshold of CAD 50,000 per QALY, for each of the four cohorts studied.

In the base-case, upfront AI was a cost-effective option in the very high-risk cohort, while sequential TAM-AI appears to have been the cost-effective strategy in the low-, average- and high-risk cohorts.

The results of the sensitivity analyses showed that sequential TAM-AI appears to have been the cost-effective strategy in most of the scenarios examined, especially for the low- and average-risk cohorts. In addition, incorporating adverse events into the model resulted in the upfront AI strategy becoming cost-effective in the high-risk cohort.

**Authors’ conclusions**
Upfront aromatase inhibitor (AI) appears to have been a cost-effective option in very high-risk patients, while sequential tamoxifen and aromatase inhibitor (TAM-AI) was the most cost-effective option for low- and average-risk patients. The cost-effective strategy in high-risk patients was dependent on the scenarios examined.

**CRD COMMENTARY - Selection of comparators**
A justification was given for using sequential TAM-AI as the comparator. Most recent AI trials had compared upfront AI with sequential TAM-AI strategies. You should decide if the comparator used represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The parameters used in the model were derived from published research. The paper did not state whether a systematic review of the literature was undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. The authors provided very few details of the methods used in the review of the literature. It was not stated how the results from the literature and trials were combined to give estimates of parameters. In addition, the impact of differences between the identified studies was not taken into account when estimating effectiveness. Some estimates of effectiveness were based on authors' assumptions, although the authors did not provide any justification for their choice of assumptions. Sensitivity analyses were conducted to improve the internal validity of the study.

**Validity of estimate of measure of benefit**
The estimation of health benefit (QALYs) was derived appropriately using a Markov model. The benefits were appropriately discounted. The utilities used to derive QALYs were taken from the published literature, but no details of the valuation methods were given.

**Validity of estimate of costs**
The analysis of the costs was performed from the perspective of the direct payer. All the relevant categories of costs, as well as all relevant major costs, appear to have been included in the analysis. The costs were derived from published...
sources and were inflated to a common price year. The price year was appropriately reported, which will aid any future inflation exercises. Since the costs were incurred over a long time period, discounting was relevant and was performed appropriately. The authors undertook a series of two-way sensitivity analyses in which they varied the downstream costs and increased the QALY threshold. The unit costs and the resource quantities were not reported separately, which will limit the generalisability of the results. Further, the costs and benefits incurred by patients in the two treatment arms were not reported, nor were the actual results of the incremental cost-utility ratios. Consequently, it is unclear whether the cost-utility ratios were high or low.

**Other issues**
The authors reported that other cost-utility analyses had reported a favourable cost per QALY gained for AI strategies compared with 5 years of TAM. The issue of generalisability to other settings was partly addressed through the sensitivity analysis. The authors do not appear to have presented their results selectively and the results reflected the scope of the analysis. The authors reported a number of further limitations to their study. First, key assumptions were made to reduce the infinite number of possible clinical outcomes to allow a feasible analysis. Second, a large meta-analysis would be required to test the assumption that the relative efficacy of each of the AI strategies was constant across cohorts. Finally, the analysis was based on a Canadian setting, which might not necessarily apply to other health care systems.

**Implications of the study**
The authors reported that their model may help health care providers select the cost-effective adjuvant AI strategies, at least until further direct evidence and longer follow-up is available from randomised clinical trials.

**Source of funding**
Supported by a grant from the Capital Health Research Fund.

**Bibliographic details**

**PubMedID**
17095569

**DOI**
10.1093/annonc/mdl410

**Other publications of related interest**
Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information.


**Indexing Status**
Subject indexing assigned by NLM
MeSH
Antineoplastic Agents, Hormonal /economics /therapeutic use; Aromatase Inhibitors /economics /therapeutic use; Breast Neoplasms /drug therapy /economics /psychology; Chemotherapy, Adjuvant; Cost of Illness; Cost-Benefit Analysis; Drug Costs; Female; Humans; Markov Chains; Middle Aged; Models, Economic; Nitriles /economics /therapeutic use; Postmenopause; Quality of Life; Quality-Adjusted Life Years; Tamoxifen /economics /therapeutic use; Treatment Outcome; Triazoles /economics /therapeutic use

AccessionNumber
22007000494

Date bibliographic record published
31/10/2007

Date abstract record published
31/10/2007