Cost-utility of adjuvant hormone therapies with aromatase inhibitors in post-menopausal women with breast cancer: upfront anastrozole, sequential tamoxifen-exemestane and extended tamoxifen-letrozole

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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 study examined three adjuvant hormonal strategies with aromatase inhibitors (AIs) for postmenopausal women with breast cancer (BC). The strategies were upfront AI, sequential tamoxifen-aromatase inhibitor (TAM-AI) and extended TAM-AI. A strategy of TAM alone was also considered. TAM alone was given at a dose of 20 mg daily for 5 years. Upfront AI (anastrozole, ANA) was given at a dose of 1 mg daily for 5 years. Sequential TAM-AI consisted of TAM for 2.5 years followed by exemestane (EXE) at a dose of 25 mg daily for 2.5 years. Extended TAM-AI comprised of 5 years of TAM followed by letrozole (LET) at a dose of 2.5 mg daily for 3 years.

Type of intervention
Treatment (adjuvant).

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of postmenopausal women with hormone receptor positive BC who had undergone curative surgery.

Setting
The setting was a hospital. The economic study was carried out in Belgium.

Dates to which data relate
The clinical data were derived from studies published between 2003 and 2006. No dates for the resource use data were reported. The price year was 2005.

Source of effectiveness data
The clinical and epidemiological data used in the model were:

- the hazard ratios associated with treatments (hazard ratios of disease-free survival for AI strategies compared with TAM alone),
- the proportion of node-negative patients,
- the rate of BC recurrence,
- the proportion of distant and local recurrences,
the switch rates among therapies, survival, and the relative risks of adverse events.

**Modelling**
A published Markov model was updated to include the strategy of extended AI. The time horizon of the model was 20 years. Women entered the model at 60 years of age and could receive one of the four strategies over the next 5 years (8 years for extended TAM-AI). The health states and possible transitions between health states were explicitly described and a schematic of the model was presented. The cycle length was not explicitly reported.

**Sources searched to identify primary studies**
The data were mainly derived from three randomised clinical trials (RCTs): the ATAC trial (arimidex, tamoxifen alone or in combination), the International Exemestane Study (IES) and MA17 trials. Details of each trial were given. Such details included the treatments compared, the sample size (6,241, 4,724 and 5,187 for the three studies, respectively), patient follow-up and key results. Some assumptions were also made, mainly in order to extend the 5-year trial results to a longer time horizon. Survival came from Belgian life tables.

**Methods used to judge relevance and validity, and for extracting data**
No systematic search for data was reported. However, the authors selected the largest and most representative trials that compared the three adjuvant hormonal strategies with AIs. Since no head-to-head trial was found, an indirect comparison was made with TAM as the common comparator. Clinical estimates for TAM alone were combined by weighted average.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were estimated using the decision model analysis. Expected survival was combined with utility weights derived from a published source, the CEA Registry (2005) Tufts-New England Medical Center, Institute for Clinical Research and Health Policy Studies. Utility weights were reported, but no information on the methods and instruments used to obtain these estimates were given. The benefits were discounted at an annual rate of 3%.

**Direct costs**
The analysis was carried out from the viewpoint of the third-party payer. It included the costs of drugs, follow-up, cancer recurrence management and the treatment of side-effects. A breakdown of the cost items was not given. The unit costs and quantities of resources used were not presented separately for all items, but monthly costs for each drug were provided. The costs were estimated using the wholesale acquisition costs for drugs and a Belgian cost study for the other items. The source of the resource use data was unclear but the probabilities of events were taken from the three main clinical trials. Discounting was relevant, as long-term costs were evaluated, and an annual discount rate of 3% was applied. The price year was 2005.

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

**Indirect Costs**
Productivity costs were not considered.
**Currency**
Euros (EUR).

**Sensitivity analysis**
A secondary analysis was run by substituting the hazard ratios of disease-free survival with time-to-recurrence hazards. The robustness of the cost-utility ratios to variations in other model inputs was investigated in one-way threshold analyses and two-way sensitivity analyses. The validity of the model was also tested using data from the RCTs. The sources of alternative values were not explicitly reported, although hazard ratios were varied within their published confidence intervals.

**Estimated benefits used in the economic analysis**
In a hypothetical cohort of 1,000 women, the expected QALYs were 11,535 with TAM alone.

The additional QALYs gained with the other three treatments over TAM were 231 with upfront AI, 251 with TAM-EXE and 150 with TAM-LET. Thus, when the three AI strategies were compared, upfront AI produced 82 additional QALYs over TAM-LET, TAM-EXE produced 102 additional QALYs over TAM-LET, while upfront AI generated 20 fewer QALYs over TAM-EXE.

**Cost results**
In a hypothetical cohort of 1,000 women, the expected costs were EUR 24,033,083 with TAM alone.

The additional costs associated with the other three treatments over TAM were EUR 4,616,587 with upfront AI, EUR 1,250,699 with TAM-EXE and EUR 1,574,270 with TAM-LET. Thus, when the three AI strategies were compared, upfront AI led to an additional cost of EUR 3,042,317 over TAM-LET, TAM-EXE produced cost-savings of EUR 323,571 over TAM-LET, and upfront AI generated an additional cost of EUR 3,365,888 over TAM-EXE.

**Synthesis of costs and benefits**
Incremental cost-utility ratios were calculated in order to combine the costs and benefits of the alternative strategies.

The incremental cost per QALY gained in comparison with TAM alone was EUR 19,982 with upfront AI, EUR 4,976 with TAM-EXE and EUR 10,530 with TAM-LET.

An incremental comparison among the three AI strategies showed that TAM-EXE was the dominant option (both more effective and less expensive). In the comparison between upfront AI and TAM-LET, the incremental cost per QALY gained with upfront AI was EUR 37,313, which was marginally unfavourable given a cost-utility threshold of EUR 30,000.

The secondary analysis confirmed most of the results of the primary analysis. The incremental cost per QALY of the three AI strategies was around EUR 10,000 compared with TAM alone, while TAM-EXE dominated TAM-LET. However, upfront AI was the most effective strategy, with an incremental cost-utility ratio of EUR 13,103 over TAM-LET and EUR 33,786 over TAM-EXE.

The other sensitivity analyses suggested that a key factor of the model was the duration of benefit beyond the end of adjuvant therapy. If no carryover effect was assumed, then less favourable cost-utility ratios were observed in comparison with TAM alone, especially for the upfront AI strategy (over EUR 30,000 per QALY).

The results of the other sensitivity analyses indicated that the base-case results were quite robust, except for the scenario in which the hazard ratio for disease-free survival for upfront AI was set at the upper value (in this case, the incremental cost per QALY gained over TAM alone exceeded the EUR 30,000 threshold). The model was successfully validated.
Authors' conclusions
All three aromatase inhibitor (AI) strategies were cost-effective in comparison with tamoxifen (TAM) alone as adjuvant treatment of post-menopausal women with breast cancer (BC). Sequential TAM-AI was the preferred strategy among the three adjuvant hormonal treatments.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear in that the three available AI strategies were compared, not only with each other but also with the TAM alone option. The dosages and duration of treatment were stated clearly. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The authors justified the choice of the three RCTs as the largest and most representative comparisons of the three strategies. However, the use of data from ongoing as well as other published RCTs was taken into account in the sensitivity analysis. Some information on the primary RCTs (study sample, length of follow-up) was given. Thus, although no systematic search for data was undertaken, the choice of the clinical inputs was valid given the selection of robust sources such as RCTs, which usually have a high internal validity. However, a limitation of the analysis was the requirement for an indirect comparison technique between treatments since the available RCTs shared TAM alone as the unique comparator.

Validity of estimate of measure of benefit
Benefits (QALYs) were modelled using a Markov model, which was appropriate given the cyclic nature of the disease. The estimates of utility weights used to calculate QALYs were reported, but no detailed information on the methodology used to derive these values was provided. Discounting was appropriately performed.

Validity of estimate of costs
Information on the cost analysis was limited given that most of the details had been reported in a previous model. However, the cost categories included were consistent with the perspective stated in the study. Some costs were not broken down but were presented as macro-categories, and this may limit the possibility of replicating the analysis in other settings. The sources of the data were reported and these reflected the Belgian health care system. The use of alternative discount rates and cost estimates was investigated in the sensitivity analysis, the results of which were only presented graphically (tornado diagram). The price year was explicitly stated, which has important implications for the generalisability of the study results.

Other issues
The authors reported the findings from other studies and stated that similar results were found in the current economic evaluation for the Belgian setting. The issue of the generalisability of the study results to other settings was implicitly addressed in the extensive sensitivity analysis. The results of the analysis were satisfactorily reported, although some of them were only presented by means of graphs. The study referred to postmenopausal women with early BC and this was reflected in the authors' conclusions.

Implications of the study
The study results support the use of adjuvant hormonal therapy incorporating AI strategies as a cost-effective alternative to hormonal therapy with TAM alone for postmenopausal women with BC. The availability of results from ongoing RCTs performing head-to-head comparisons of the different hormonal treatments would allow a more sound evaluation of their cost-effectiveness.

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Other publications of related interest
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Lonning PE. Comparing cost/utility of giving an aromatase inhibitor as monotherapy for 5 years versus sequential administration following 2-3 or 5 years of tamoxifen as adjuvant treatment for postmenopausal breast cancer. Ann Oncol 2006;17:217-25.


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