Hormonal therapies for early breast cancer

Hormonal therapies for early breast cancer: systematic review and economic evaluation

D Hind,[1*] S Ward,[1] E De Nigris,[1] E Simpson,[1] C Carroll[1] and L Wyld[2]

[1] The School of Health and Related Research (ScHARR), University of Sheffield, UK
[2] Surgical Oncology, University of Sheffield, UK

* Corresponding author

Executive summary

Health Technology Assessment 2007; Vol. 11: No. 26

Health Technology Assessment
NHS R&D HTA Programme
www.hta.ac.uk

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Executive summary

Description of proposed service

Aromatase inhibitors (AIs) are proposed for the adjuvant treatment of oestrogen receptor-positive early breast cancer in postmenopausal women in three different indications: (1) instead of the current anti-oestrogen treatment, tamoxifen, for 5 years ('primary adjuvant'); (2) instead of tamoxifen for 2–3 years of an adjuvant programme, implemented opportunistically after a woman survives disease free for a period on tamoxifen ('unplanned switching strategy'), or planned from the time of surgery ('planned sequence strategy'); (3) for 3–5 years in women who are disease free following 5 years of tamoxifen: this is known as an 'extended adjuvant' strategy. The three AIs and their licensed indications are (1) anastrozole (primary adjuvant), (2) letrozole (primary adjuvant, extended adjuvant) and, (3) exemestane (unplanned switching).

Epidemiology and background

Around 23,000 postmenopausal women will be diagnosed with oestrogen receptor-positive early breast cancer every year. Treated with tamoxifen, disease will have recurred in about one-quarter after 5 years with recurrences continuing up to 20 years after surgery.

Objectives of the review

The objectives of this review were to establish the clinical and cost-effectiveness of aromatase inhibitors (AIs) anastrozole, letrozole and exemestane compared with tamoxifen in the adjuvant treatment of early oestrogen receptor-positive breast cancer in postmenopausal women with oestrogen receptor-positive early-stage breast cancer.

Methods

Fourteen electronic bibliographic databases and three trials registers were searched from May to June 2005. Three conference abstract databases were searched in December 2005. Studies evaluating the clinical effectiveness of AIs against 5 years' tamoxifen treatment were included and critically appraised on the adequacy of allocation concealment, randomisation, double blinding and intention-to-treat analysis. Critical appraisal and data extraction into standardised forms were performed independently, unblinded, by two researchers.

Three strategies for the proposed use of AIs were considered. First, primary adjuvant therapy, comparing AIs with tamoxifen in treatment of patients randomised at zero years after surgery. Second, unplanned switch therapy, patients randomised following 2–3 years of tamoxifen to either continue on tamoxifen for the remainder of the 5-year adjuvant treatment period or switch to an AI. Third, extended/sequential adjuvant therapy, patients randomised after 5 years of tamoxifen to receive 5 years of further treatment on an AI or placebo.

The three treatment strategies were considered separately within the economic analysis. Trials with strategies that randomised patients half-way through or at the end of the standard 5-year adjuvant treatment period with a strategy which randomised patients immediately after surgery were not compared directly.

The independent economic analysis used a state transition (Markov) approach to simulate the disease outcomes of patients up to a time horizon of 35 years post-surgery for early breast cancer. The primary outcome of interest was the cost per quality-adjusted life-year (QALY) gained, associated with AIs versus tamoxifen (or placebo, in the case of the extended adjuvant setting).

HRs from the trials were applied to the tamoxifen event rates to estimate event rates in the aromatase inhibitor arm.

Costs of health states were based on a review of published evidence to obtain the most recent and appropriate costs. Where published data were not identified, clinical opinion was sought. First-year costs and subsequent-year costs are assigned for each of the different health states modelled. Costs of managing adverse events are modelled. ▶

The utility of the disease-free population was adjusted for age, based on data from Kind and Dolan. A literature review was undertaken in order to identify utility estimates for health states within the model. These were used as multipliers to adjust the age-related utility of the general population following an event. It is assumed that there is no disutility for patients on AIs or tamoxifen.

Results

Number and quality of studies and direction of evidence

Seven Phase III randomised controlled trials of varying methodological quality were found. Meta-analysis of studies was prohibited by the heterogeneity of trial designs. As most of the study populations had a relatively good prognosis and events are rare, hazard ratios (HRs) with 95% confidence intervals (CIs) and absolute risk reductions (ARRs) are presented.

A meta-analysis of three trials found a significant difference in overall survival when an unplanned anastrozole switching strategy was compared with 5 years' tamoxifen (details academic-in-confidence). Significant improvements in overall survival are yet to be demonstrated in other strategies. Compared with 5 years' tamoxifen, disease-free survival (disease recurrence or death from any cause) was significantly improved: in the primary adjuvant setting with anastrozole (68 months' follow-up: HR 0.87, 95% CI 0.78 to 0.97; ARR 0.024) and letrozole (26 months' follow-up: HR 0.83, 95% CI 0.73 to 0.94; ARR 0.019), and with an exemestane switching strategy (31 months' follow-up: HR 0.68, 95% CI 0.56 to 0.82; ARR 0.035). Other trials did not report this outcome. Breast cancer recurrence (censoring death as an event) was significantly improved with primary adjuvant anastrozole (68 months' follow-up: HR 0.79, 95% CI 0.70 to 0.90; ARR 0.031) and letrozole (26 months' follow-up: HR 0.74, 95% CI 0.64 to 0.87; ARR 0.021), anastrozole switching (28 months' follow-up: HR 0.59, 95% CI 0.44 to 0.81; ARR 0.027): extended adjuvant anastrozole (60 months' follow-up: HR 0.64, 95% CI 0.41 to 0.99; ARR 0.042) or letrozole (30 months' follow-up: HR 0.58, 95% CI 0.45 to 0.76; ARR 0.024). The AIs and tamoxifen have different side-effect profiles, with tamoxifen responsible for small but statistically significant increases in endometrial cancer and, sometimes, thromboembolic events and stroke. AIs show a trend towards increases in osteoporosis, the statistical significance of which increases with follow-up time. The absence of tamoxifen treatment also increases the risk of hypercholesterolaemia and cardiac events in women of this age. There was no significant difference in overall health-related quality of life between standard treatment and either primary adjuvant anastrozole and extended adjuvant letrozole strategies.

Cost-effectiveness results

The cost-effectiveness results for anastrozole and letrozole, compared with tamoxifen in the primary adjuvant setting, were estimated to be £32,000 and £21,600 per QALY, respectively, based on an analysis over 35 years. There is, however, greater uncertainty around the results for letrozole, as the hazard ratio is based on an average follow-up of 26 months, compared with 68 months for anastrozole. There is currently no trial evidence for exemestane in this setting.

The cost-effectiveness results in the unplanned switching setting for anastrozole and exemestane, compared with tamoxifen, were estimated to be £23,200 and £19,200 per QALY, respectively, based on an analysis over 35 years. There is currently no trial evidence for letrozole in this setting.

In the extended adjuvant setting, the cost per QALY for letrozole compared with placebo was estimated to be £9800, based on an analysis over 35 years.

All these results were considered to be conservative. In the base case it was assumed that the benefits of AIs over tamoxifen or placebo seen during the therapy period were gradually lost during the following 10 years. In other words, the rate of recurrence for AIs after the trial period was assumed to be higher than that for tamoxifen between 5 and 15 years post-surgery, to the extent that by year 15 the number of patients in a disease-free state was the same in both arms. An alternative scenario, the 'benefits maintained' scenario, was tested in sensitivity analysis. In this scenario, it was assumed that following the treatment period the annual rate of recurrence in both arms would be the same. This reduced the cost-effectiveness ratio by over 50%, to around £10,000–12,000, £5000 and £3000 in the primary adjuvant, unplanned switching and extended adjuvant setting, respectively. The limited evidence to date of benefits after the therapy period suggested that the 'benefits maintained' scenario may be realistic.

▶

One-way and probabilistic sensitivity analysis suggested that these results were generally robust to changes in the key model parameters. Understanding of the long-term treatment effects is, however, incomplete. The economic model considered costs and benefits over the lifetime of a patient, requiring extrapolation of these costs and benefits well beyond the timeframe of the reported trial outcomes to date. Data on the impact of AIs on survival are awaited from the majority of the trials to confirm whether or not the benefits seen in disease-free survival and recurrence rates are translated into overall survival benefit in the medium to long term. The largest uncertainty in terms of adverse events relates to the future risk of fracture in the period following adjuvant therapy, as the treated population gets older

The results from the economic analyses within the industry submissions were generally lower than the results from the authors' model and were close to or below £12,000 in all three settings. The authors' analyses generally produced a lower estimate of QALY gain for the aromatase inhibitors, due to the more conservative assumption regarding benefits, along with differences in the utility values used in the economic model.

Conclusions

Clinical effectiveness

No individual study reported a difference in overall survival between any AI and tamoxifen (or placebo in the extended adjuvant setting). An unpublished meta-analysis of individual patient data from three trials did find a significant difference in overall survival when unplanned anastrozole switching strategy was compared with 5 years' tamoxifen. Compared with 5 years' tamoxifen, DFS (absence of disease recurrence or death from any cause) was significantly increased in the primary adjuvant setting (using anastrozole or letrozole) and the unplanned switching strategy (using anastrozole or exemestane). Breast cancer recurrence (censoring death as an event) was significantly improved with primary adjuvant anastrozole or letrozole, an anastrozole or exemestane unplanned switching strategy and an extended adjuvant anastrozole or letrozole strategy. There is no evidence that AIs confer any advantage in overall health-related quality of life. On the basis of the current data and within their licensed indications, AIs can be considered clinically effective compared with standard tamoxifen treatment. However, their long-term effects, in terms of both benefits and harms, remain unclear.

Cost-effectiveness

Three treatment strategies for AIs – primary adjuvant therapy, unplanned switch therapy and extended adjuvant therapy – were considered separately within the economic analysis. Under the conservative assumption that benefits gained by AIs during the treatment period are gradually lost over the following 10 years, the cost per QALY for AIs compared with tamoxifen is estimated to be between £21,000 and £32,000 in the primary adjuvant setting and around £20,000 in the unplanned switch setting. The cost per QALY for AIs compared with placebo in the extended adjuvant setting is estimated to be around £10,000. Under the less conservative assumption that rates of recurrence are the same in both arms after the therapy period is complete, the incremental cost-effectiveness ratios are typically at least 50% lower, suggesting that AIs are likely to be considered cost-effective in all three settings. However, understanding of the long-term treatment effects on cost-effectiveness is incomplete.

Need for further research

Randomisation of populations at any point other than the start of treatment programmes should be strongly discouraged in future trials as it limits the utility of the resulting dataset. In the present case, this means randomising at the start of, not half way through or at the end of, the adjuvant period, because the objective is the same from successful surgery until relapse or death.

Data on the impact of AIs on survival are awaited from the majority of the trials to confirm whether or not the benefits seen in disease-free survival and recurrence rates are translated into overall survival benefit in the medium to long term.

Long-term follow-up data on major adverse events, including cholesterol levels, cardiovascular events and fracture rates, are awaited. Evidence to date suggests that the impact of these adverse events does not unduly impact on the cost-effectiveness ratios. The long-term implications for the costs and benefits of AIs and tamoxifen will need to be reviewed as and when new information becomes available.

Publication

Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L. Hormonal therapies for early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(26).

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

Criteria for inclusion in the HTA monograph series

Reports are published in the HTA monograph series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/20/01. The protocol was agreed in June 2005. The assessment report began editorial review in July 2006 and was accepted for publication in October 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.