Aromatase inhibitor versus tamoxifen in postmenopausal woman with advanced breast cancer: a literature-based meta-analysis

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CRD summary
The authors concluded that overall response and clinical benefit rates in postmenopausal women with advanced breast cancer were better with aromatase inhibitor treatment than with tamoxifen; the adverse events with aromatase inhibitors were not inferior to tamoxifen. Potential methodological limitations in the review mean that the reliability of the review is unclear.

Authors' objectives
To evaluate the efficacy and toxicity profile of aromatase inhibitors compared with tamoxifen as a first-line hormonal therapy for postmenopausal women with advanced breast cancer.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov were searched from 1966 to December 2009 for published articles in English. Search terms were reported. Reference lists were scanned and principal investigators were contacted to locate further studies.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that evaluated third generation aromatase inhibitors compared with tamoxifen as first-line treatment for postmenopausal women with histologically-confirmed advanced breast cancer. The primary outcomes of interest were overall response rate (percentage of patients with a complete or partial tumour response) and clinical benefit (percentage of patients with complete or partial response, or stable disease). Secondary outcomes were overall survival (time between the date of randomisation and death, or last follow-up date for censored patients according to World Health Organisation criteria), and incidence of adverse events (including hot flushes, nausea, bone pain, vaginal bleeding, and thromboembolic events, using National Cancer Institute criteria).

The aromatase inhibitors in included trials were exemestane, letrozole, and anastrozole. The age of participants ranged from 31 to 96 years.

Two reviewers agreed on the selection of trials for inclusion.

Assessment of study quality
The authors did not state that they assessed trial quality.

Data extraction
Data were extracted to enable the calculation of odds ratios (OR) and 95% confidence intervals (CI). Median values were used for time to progression and overall survival. Overall survival was calculated using intention-to-treat data.

Two reviewers independently extracted the data, and results were verified by comparison.

Methods of synthesis
Odds ratios were pooled in a fixed-effect meta-analysis, unless heterogeneity (measured by Q statistic and I²) was detected, in which case a random-effects model was used. Subgroup analysis on overall response by oestrogen/progesterone receptor status was reported. Publication bias was assessed using a funnel plot and Egger’s test.

Results of the review
Six RCTs (2,657 patients) were included in the review.

There was a significant difference in favour of aromatase inhibitors for overall response rate (OR 1.56, 95% CI 1.17 to
2.07; six trials; Ι²=58.1%) and clinical benefit (OR 1.70, 95% CI 1.24 to 2.33, six trials; Ι²=70.2%). There was no significant difference between groups for the analysis of overall survival (three trials) or response by oestrogen/progesterone receptor status (three trials).

Significantly more adverse events were reported in the tamoxifen group for vaginal bleeding (OR 0.30, 95% CI 0.16 to 0.56; four trials) and thromboembolic events (OR 0.47, 95% CI 0.28 to 0.77, three trials) with no significant heterogeneity. No other statistically significant results were found for adverse events.

There was no evidence of publication bias (results not shown).

**Authors' conclusions**
Aromatase inhibitors had better overall response and clinical benefit rates than tamoxifen; they were not inferior to tamoxifen for toxicity.

**CRD commentary**
The review question was clear. Inclusion criteria were sufficiently detailed to allow replication. Relevant data sources were searched but language restrictions meant that the potential for missing studies could not be ruled out. Processes for the selection of studies and data extraction were conducted with attempts to minimise error and bias.

There was no reported quality assessment of trials, so their reliability was uncertain. Trial details were provided. Statistical heterogeneity was assessed. Given the high heterogeneity in the analysis of clinical benefit, it was questionable whether statistical synthesis was appropriate. The authors acknowledged that the results should be interpreted with care.

The authors' conclusion reflects the evidence presented, but potential methodological limitations mean that the reliability of the review is unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that aromatase inhibitors were recommended instead of tamoxifen for postmenopausal women with hormone receptor-positive advanced breast cancer.

**Research:** The authors stated that further prospective randomised controlled trials were necessary.

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