A qualitative systematic review of the evidence base for non-cross-resistance between steroidal and non-steroidal aromatase inhibitors in metastatic breast cancer

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CRD summary
This review concluded that switching to the steroidal aromatase inhibitor exemestane after failure of the non-steroidal aromatase inhibitors anastrozole, letrozole and aminoglutethimide in patients with metastatic breast cancer was a reasonable option. Potential limitations in the review process, limited evidence and uncertainties about study quality mean the authors’ conclusions should be treated with caution.

Authors’ objectives
To evaluate the safety and efficacy of steroidal and non-steroidal aromatase inhibitors in patients with metastatic breast cancer who had progressed/relapsed after previous adjuvant treatment.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched for publications in English; search terms were not reported. Search dates were not stated, but the included studies were published between 1997 and 2008. The bibliography each retrieved article and relevant reviews were handsearched. Only full publications were considered.

Study selection
Randomised and non-randomised controlled trials that assessed the cross-resistance, efficacy and safety of steroidal and non-steroidal aromatase inhibitor (SAI and NSAI) treatments for postmenopausal women with advanced metastatic breast cancer were eligible for inclusion. Treatments could be used either in sequence or as third-line adjuvant therapy. Metastases had to be confirmed by histology/cytology. Patients needed to have progressed/relapsed from previous adjuvant first-line or second-line SAI/NSAI treatment and undergone treatment with at least two regimens of aminoglutethimide, anastrozole, letrozole and/or exemestane.

Most of the included studies were uncontrolled observational studies. Almost all studies were of treatment with a SAI (exemestane) after failure of treatment with a NSAI (where given, mostly letrozole and/or anastrozole, and also aminoglutethimide); one study additionally reported on treatment with a NSAI (letrozole/anastrozole) after a SAI (exemestane/formestane). One study was of treatment with an NSAI (anastrozole) after treatment with a different NSAI (aminoglutethimide). The main clinical outcomes reported were clinical benefit, complete and partial response, stable disease, progressive disease and overall response rate. Clinical benefit was defined as complete response plus partial response plus stable disease/no change after at least 24 weeks. Safety and tolerability outcomes were reported and included mortality, discontinuation of treatment due to toxicity and adverse events.

The authors did not report how many reviewers performed the selection.

Assessment of study quality
There was no formal validity assessment.

Data extraction
The numbers of events for each outcome were extracted to enable calculation of percentages for each patient group. Time to progression was extracted.

The authors did not report how many reviewers performed data extraction.

Methods of synthesis
A narrative synthesis was provided. Results were summarised for: treatment with an SAI after failure with an NSAI; treatment with an NSAI after an SAI; and treatment with an NSAI after failure with a different NSAI. Data for
formestane were not included in the synthesis.

**Results of the review**

Ten studies were identified (n=1,457 participants, range 27 to 693): one double-blind randomised controlled trial (RCT) (n=693), three non-randomised comparative studies (n=410, range 30 to 299) and six single-arm observational studies (n=354, range 27 to 108).

**Efficacy of SAI after NSAI (nine studies):** The clinical benefit of exemestane after NSAI ranged from 12% to 55% (nine studies). Complete response to exemestane after NSAI ranged from zero to 6% (six studies). Partial response ranged from 2% to 23% (six studies). Overall response rate ranged from 2% to 26% (six studies). Stable disease after at least 24 weeks ranged from 10% to 47% with exemestane (seven studies). Time to progression with exemestane ranged from 3.7 months to 5.2 months (three studies). One study reported median survival time as 15.2 months.

**Efficacy of NSAI after SAI (one study):** The clinical benefit of NSAI after SAI was 55%.

**Efficacy of NSAI after NSAI (one study):** The overall response rate for anastrozole after aminoglutethimide was 18% with a stable disease rate of 41% after at least eight weeks.

**Safety of SAI after NSAI (nine studies):** The authors reported no drug-related deaths for three studies, but Table 4 reported 10% mortality for one study. Discontinuation of treatment due to toxicity ranged from zero to 3% (five studies). Adverse events ranged from 24% to 77% (five studies). The most common adverse events were nausea, fatigue, hot flushes, dizziness, weakness, sweating, androgenic symptoms and peripheral oedema. Serious drug-related adverse events were reported in 1% of patients in one study.

**Safety of NSAI after SAI (one study):** Adverse events were reported in 28% patients.

**Safety of NSAI after NSAI (one study):** Results for the patients in this study were unclear.

The one RCT compared treatment with exemestane with fulvestrant and found no significant differences.

**Authors’ conclusions**

This review suggested that switching from a NSAI to a SAI in patients with metastatic breast cancer was a reasonable option.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched for studies published in English. It appeared that unpublished studies were not considered and so some relevant studies may have been missed. No search terms were reported, so the quality of the search was uncertain. Publication bias was not assessed. No formal validity assessment was performed and little relevant information was provided to allow assessment of study quality.

There was an apparent discrepancy between the reported inclusion criteria (randomised and non-randomised controlled trials) and the included studies (mostly uncontrolled observational studies). Most of the included studies were small and there was only one RCT. The authors did not report any efforts to reduce error and bias during the review process. Some relevant study details were reported. A narrative synthesis was performed. Insufficient study details were provided to allow clarification of whether the results summary was correct.

Potential limitations in the review process and uncertainties about the quality of the included studies mean the authors’ conclusions should be treated with caution.

This review was funded by Pfizer Ltd and two of the authors were employed by the company.

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

**Practice:** The authors suggested that switching from a NSAI to a SAI in patients with metastatic breast cancer would be
particularly important for those who would probably respond to further endocrine manoeuvres, namely those with strongly oestrogen receptor-positive disease, non-visceral disease, a good prior response or a long response duration. This would also avoid potential side effects of cytotoxic chemotherapy.

**Research:** The authors identified a need for further research to optimise the sequence of endocrine therapies and other possible treatments (such as fulvestrant, tamoxifen, megestrol acetate) in metastatic breast cancer.

**Funding**
Pfizer Ltd.

**Bibliographic details**

**PubMedID**
21134732

**DOI**
10.1016/j.clon.2010.11.005

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antineoplastic Agents, Hormonal /therapeutic use; Aromatase Inhibitors /therapeutic use; Breast Neoplasms /drug therapy; Chemotherapy, Adjuvant /methods; Female; Humans; Steroids /therapeutic use; Treatment Outcome

**AccessionNumber**
12011002024

**Date bibliographic record published**
22/06/2011

**Date abstract record published**
26/10/2011

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.