Fulvestrant in the treatment of advanced breast cancer: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review concluded that fulvestrant had a good tolerability profile and efficacy that was similar to other hormonal agents for treatment of advanced breast cancer. The authors’ conclusions reflected the evidence, but they should be viewed with caution given the small number of included trials and the potential for reviewer error and bias.

Authors’ objectives
To compare the efficacy and tolerability of fulvestrant versus standard treatments (aromatase inhibitors and tamoxifen) for patients with advanced breast cancer.

Searching
MEDLINE, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles in any language up to August 2008. Search terms were reported. Reference lists of relevant trials were handsearched. Further searches involved scanning of symposia proceedings, poster presentations, and abstracts from major cancer meetings (e.g. American Society of Clinical Oncology Annual meetings, San Antonio Breast Cancer Symposium).

Study selection
Randomised controlled trials (RCTs) that compared fulvestrant versus other hormonal therapies in patients with advanced breast cancer were eligible for inclusion. Single arm and dose-escalation trials were excluded.

Primary outcomes were overall survival, time to tumour progression, objective response and clinical benefit. Objective response was defined as the proportion of patients with complete response or partial response after treatment. Clinical benefit was defined as the proportion of patients with an objective response or stable disease lasting at least 24 weeks. Secondary outcomes were the number of adverse events.

Included trials enrolled postmenopausal breast cancer patients whose reported median age was 63 to 67 years. Fulvestrant was administered as a 250mg (intramuscular) preparation once a month in all included trials. Fulvestrant was the first line therapy in one trial and second or greater in the remaining trials. Comparators included anastrozole, exemestane and tamoxifen.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Trial quality assessed randomisation, allocation concealment, subject withdrawals and reasons for withdrawals, interim analyses, and intention-to-treat analyses.

The authors did not state how many reviewers assessed trial quality.

Data extraction
Data to enable the calculation of hazard ratios (HRs) for overall survival and time to progression outcomes and odds ratios (ORs) for clinical benefit, objective response and all secondary outcomes, with 95% confidence intervals (CIs), were extracted using 2x2 tables.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Heterogeneity was assessed using $X^2$ statistic. Where there was no evidence of heterogeneity, pooled hazard ratios and 95% confidence intervals were calculated using the Peto method; pooled odds ratios and 95% confidence intervals were calculated using the Mantel-Haenszel method. Where evidence of heterogeneity was found, pooled effect sizes, with 95% confidence intervals, were calculated using the DerSimonian and Laird random-effects method. Standard errors of hazard ratio estimates were indirectly derived from the confidence intervals reported in each trial.

**Results of the review**

Four RCTs (eight reports) were included in the review (n=2,125 patients, table 1; range 400 to 693). Trial quality was varied: only one trial described the method of randomisation and allocation concealment; three trials were double-blinded; three trials described withdrawals; and none of the trials were stopped early.

No statistically significant differences were found between fulvestrant and other hormonal agents for overall survival, time to progression, clinical benefit, objective response rate or adverse events (three RCTs each).

The incidence of joint disorders was significantly higher in patients receiving hormonal agents other than fulvestrant (pooled OR 0.621, 95% CI 0.424 to 0.909; three RCTs; n=1,544 patients).

**Authors' conclusions**

Fulvestrant has a good tolerability profile and efficacy that was similar to other hormonal agents for treatment of advanced breast cancer.

**CRD commentary**

The review addressed a clear question with explicit study selection criteria. Several databases were searched without any restrictions on language or publication date. Efforts were made to search for unpublished studies. Consequently, language and publication biases were unlikely. It was unclear whether review processes were conducted in duplicate, so the possibility of reviewer error and bias could not be excluded.

Trial quality appeared to have been assessed using appropriate criteria. The methods used to combine data and account for statistical heterogeneity were appropriate and justified. The authors appropriately stated that a limitation of the review was the small number of included trials, with differences in design and modes of treatment.

The authors' conclusions reflected the evidence, but they should be viewed with caution given the small number of included trials and potential for reviewer error and bias.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further prospective data are needed to determine the appropriate timing and schedule for administration of fulvestrant.

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