Letrozole: a review of its use in postmenopausal women with advanced breast cancer

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Authors' objectives
To assess the use of letrozole in postmenopausal women with advanced breast cancer.

Searching
AdisBase, MEDLINE and EMBASE were searched from 1966 to 1998. AdisBase search terms were 'letrozole', 'letrazole', 'CGS-20267' and 'Femara'. Search terms for MEDLINE and EMBASE were the same as for AdisBase but also included '112809-51-5'.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Letrozole administered orally (0.5, 1, or 2.5 mg/day) as a once-daily regimen until progression of disease, compared to 500 mg/day aminoglutethimide (administered at 250 mg, twice daily) and megestrol as a single daily dose of 160 mg.

Participants included in the review
Postmenopausal women with locally, locoregionally advanced or metastatic breast cancer previously treated with an anti-oestrogen. Patients were permitted to have had no more than one chemotherapy regimen in the adjuvant or neoadjuvant setting and/or one regimen for advanced disease. Patients also had to have positive or unknown oestrogen or progesterone receptor status.

Outcomes assessed in the review
The primary outcome measure was objective response rate, assessed with the International Union Against Cancer criteria. Secondary outcomes included time to progression (the interval between start of therapy and diagnosis of progressive disease or death), time to treatment failure (the interval between start of therapy and diagnosis of progressive disease, death, withdrawal, or loss to follow-up), and overall survival time. Data regarding quality of life and adverse events were also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The two trials of letrozole were discussed and compared individually to aminoglutethimide and megestrol. Studies were not weighted and no data regarding the potential for publication bias were reported.
How were differences between studies investigated?
Differences between the studies were not investigated thoroughly.

**Results of the review**

Five randomised trials were included (n=1,297): 3 phase II trials (n=191) and 2 phase IIb/III trials (n=1,106). Phase II trials are concerned with dose findings, whilst phase IIb/III trials are concerned with efficacy. Consequently, results discussed in this abstract are from the 2 phase IIb/III trials.

Objective response: overall, 19.5 and 23.6% of patients achieved an objective response with 2.5 mg/day letrozole, compared with 12.4% of patients receiving 500 mg/day aminoglutethimide (p=0.06) and 16.4% of patients receiving 160 mg/day megestrol (p=0.04). Compared to 2.5 mg/day letrozole, 0.5 mg/day letrozole was associated with poorer response rates (p=0.004). Respective complete response rates were 4.9 and 6.9% with 2.5 mg/day letrozole, 4.7 and 3.2% with 0.5 mg/day letrozole, 1.1% with aminoglutethimide and 4.2% with megestrol. The median duration of response with letrozole (2.5 mg/day) was 24 and 33 months, compared to 15 months with aminoglutethimide and 18 months with megestrol (p=0.02).

Progression or failure time: letrozole (2.5 mg/day) was significantly superior to aminoglutethimide (risk ratio, RR 0.72, 95% confidence interval, CI: 0.57, 0.92, p=0.008), but not megestrol (RR 0.8, 95% CI: 0.62, 1.02, p=0.07). A similar analysis showed letrozole (2.5 mg/day) was significantly superior to both comparators with respect to time to treatment failure: aminoglutethimide (RR 0.7, 95% CI: 0.55, 0.88, p=0.003) and megestrol (RR 0.77, 95% CI: 0.61, 0.99, p=0.04).

Overall survival: letrozole (2.5 mg/day) was associated with an increased median survival time of 8 months compared to aminoglutethimide (RR 0.64, 95% CI: 0.49, 0.85, p=0.002), and 3 months compared to megestrol (RR 0.82, 95% CI: 0.63, 1.08, p=0.15). Letrozole 2.5 mg/day was significantly superior to the 0.5 mg/day dosage with respect to overall survival (p<0.04).

Quality of life: one trial reported quality of life data, and no major differences were observed between patients receiving letrozole and megestrol.

Adverse events: the most commonly reported adverse events judged to be related to letrozole (2.5 mg/day) were headache (1.1 and 7%), nausea (10.3 and 6%), fatigue (3.2 and 5%), hot flushes (4.9 and 5%), peripheral oedema (6%), rash (2.7%), somnolence (3.2%), vomiting (3.8%), and hypercholesterolaemia (3.8%). The majority of events were reported as mild-to-moderate in severity. Serious adverse events were reported in 10% of patients receiving letrozole (2.5 mg/day) versus 29% treated with megestrol, and in 0 versus 2.8% of aminoglutethimide recipients. No dose effect with respect to tolerability was evident with letrozole up to a dosage of 2.5 mg/day for the one trial in which this was reported.

**Authors’ conclusions**

Letrozole achieves a significantly greater duration of response than megestrol and aminoglutethimide, and longer overall survival than aminoglutethimide. Letrozole should thus be recommended as a second-line treatment for postmenopausal women with advanced breast cancer, whose disease has progressed on or failed to respond to anti-oestrogen therapy.

**CRD commentary**

The review question was general rather than specific. Inclusion criteria were not reported clearly. The literature search was reasonable, though not comprehensive, e.g. attempts to identify unpublished material were weak. A validity assessment of the primary studies was absent and methods for data analysis were poorly reported. Similarly, details of the review process were largely absent, e.g. how many reviewers were involved, whether decisions were made independently, whether reviewers were blind to source, and how disagreements were resolved.

The authors’ conclusions do follow from the presented data, although given the limitations of the review, both the results and conclusions should be treated with some caution.
Implications of the review for practice and research
Practice: The authors state that letrozole should be recommended as a second-line treatment for postmenopausal women with advanced breast cancer, whose disease has progressed or failed to respond to anti-oestrogen therapy.

Research: The authors state that direct comparisons are needed to distinguish between letrozole and other, newer aromatase inhibitors such as anastrozole and vorozole. The authors further state that the long-term tolerability profile of aromatase inhibitors needs to be detailed thoroughly.

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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.