Zoledronic acid as an adjuvant therapy in patients with breast cancer: a systematic review and meta-analysis

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**CRD summary**
The review concluded that adjuvant zoledronic acid treatment in women with breast cancer had a clear effect on fracture events and might contribute an important role on overall survival. The authors' conclusions reflect the evidence available but limitations in the search strategy, assessment of study quality and reporting of results makes it difficult to evaluate their reliability.

**Authors' objectives**
To evaluate the efficacy and safety of zoledronic acid as an adjuvant chemotherapy treatment in women with breast cancer.

**Searching**
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to December 2011 for studies in English. The search strategy was: “zoledronic acid” AND “breast cancer” AND “randomized controlled trials”. Reference lists of non-randomised controlled trials and other relevant publications and proceedings of major meetings were searched for additional studies. Study authors were contacted to identify further studies (published or unpublished).

**Study selection**
Eligible studies were randomised controlled trials (RCTs) of zoledronic acid therapy in women with breast cancer. Trials had to report on one or more of the outcomes: overall survival, disease-free survival, recurrence-free survival and other possible adverse drug-related reactions. Cross-over studies were excluded.

Mean ages (where reported) ranged from 44.5 to 61.2 years. Most studies were of patients with early-stage breast cancer; some were in patients with advanced or locally advanced disease. Where reported, 4mg of zoledronic acid was given, commonly at a frequency of every month or every six months. Comparators included unspecified non-zoledronic acid therapy, delayed zoledronic acid (in studies versus immediate treatment) or denosumab 120mg.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by group discussion.

**Assessment of study quality**
Study quality was evaluated using the Jadad scale, which appeared to have been modified but there were no details of how points were awarded. The authors stated that they assessed criteria for randomisation, allocation concealment, blinding, withdrawals/drop-outs and use of intention-to-treat analysis.

It was unclear how many reviewers performed the quality assessments.

**Data extraction**
Data were extracted in order to calculate hazard ratios (HR) or relative risks (RR) with 95% confidence intervals (CI). Authors were contacted for missing data when necessary.

Two reviewers independently extracted data. Disagreements were resolved by a third reviewer.

**Methods of synthesis**
Meta-analyses were performed to calculate pooled estimates with 95% confidence intervals using a random-effects model. Heterogeneity was assessed using the I² statistic. Sensitivity analyses were conducted to explore the effect of mean age, number of patients, disease status, control drug, duration of follow-up and Jadad score.

**Results of the review**
Seven RCTs were included (9,518 participants, range 120 to 3,360). Four trials scored 4 on the Jadad scale, two scored 3 and one scored 2. Follow-up periods ranged from 12 to 62 months.

Zoledronic acid was associated with a statistically significant improvement in overall survival (HR 0.85, 95% CI 0.73 to 1.00; three RCTs; I²=45%) but not in total death (RR 0.91, 95% CI 0.69 to 1.20; five RCTs; I²=14%). There were no statistically significant differences overall for disease-free survival (three studies; I²=75%) and recurrence free survival (three studies; I²=74%). Zoledronic acid significantly reduced the risk of disease recurrence in patients with early stage disease but significantly increased the risk in patients with advanced disease.

Zoledronic acid was associated with a significantly reduced risk of fracture (RR 0.66, 95% CI 0.52 to 0.84; six RCTs; I²=0%) but also resulted in significantly more bone pain (six RCTs), neutropenic fever (two RCTs), pyrexia (five RCTs) and rashes (two RCTs); full results and results for other drug-related adverse effects were reported.

Zoledronic acid showed significant effects on reducing risk of fracture when the mean age of the patients was less than 50, the sample size was more than 1,000, in patients with advanced breast cancer, when compared with non-zoledronic acid therapy, when the follow-up was more than 36 months and when the Jadad score was 4 or 5. No other statistically significant results were reported for the sensitivity analyses for total death and disease recurrence (results reported in the paper).

Authors’ conclusions
Zoledronic acid had a clear effect on fracture events and might contribute an important role on overall survival.

CRD commentary
The review addressed a clear question and was supported by reproducible eligibility criteria. Attempts to identify relevant studies were undertaken by searching electronic databases and checking references and conference proceedings. The very specific search strategy used, coupled with the restriction to studies in English, meant that some relevant studies may not have been identified.

Suitable methods were employed to reduce the risks of reviewer error and bias during data extraction and study selection; the authors did not report on whether such methods were used when assessing study quality. The Jadad scale was used to assess study quality and appeared to have been modified to incorporate additional criteria. The limited reporting of this, combined with the limitations associated with assessments using the Jadad scale, made it difficult to evaluate the likely reliability of individual trial results.

Very basic study details were provided. Appropriate methods were used to pool data and to assess and investigate heterogeneity. Numbers of events contributing to the analyses were not reported which made it difficult to evaluate their reliability (the likelihood of chance results).

The authors’ conclusions reflect the evidence available but limitations in the search strategy, assessment of study quality and reporting of results makes it difficult to evaluate their reliability.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that in future research of zoledronic acid it would be important to focus on patients with early-stage breast cancer or advanced breast cancer to explore the difference between these disease statuses. They suggested that ongoing trials be improved by stating that adverse effects in clinical trials should be recorded and reported normatively so that the side-effects of any treatment can be evaluated in future trials, the role of treatment duration and dosage should be investigated in more detail and survival data should be recorded in more detail.

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