Does adjuvant bisphosphonate in early breast cancer modify the natural course of the disease? A meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that available evidence did not support the hypothesis that bisphosphonates in the adjuvant treatment of early breast cancer alter the natural course of disease. Some methodological weaknesses within the review limit the reliability of the authors' conclusions.

Authors' objectives
To estimate whether the use of bisphosphonates in the adjuvant setting of breast cancer might have any effect on the natural course of the disease.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Knowledge were searched to January 2009 for articles in any language. Search terms were reported. American Society of Clinical Oncology, San Antonio Breast Cancer Symposium and European Cancer Conference were searched to January 2009. Reference lists of included studies were searched.

Study selection
Randomised controlled trials (RCTs) of bisphosphonates compared with placebo or control in patients with primary breast cancer were eligible for inclusion, irrespective of study sample size and type and dosage of bisphosphonate. The relevant primary outcomes were overall survival, disease recurrences and occurrences of bone metastases. Non-randomised trials were excluded.

The included RCTs compared pamidronate (60mg intravenously every three months or 150mg orally twice daily), zoledronic acid (4mg intravenously every 12 weeks or every six months), risendronate (30mg orally daily for two weeks) or clodronate (1,500mg intermittently intravenously for seven consecutive cycles or 1,600mg orally daily) with placebo, no treatment or delayed treatment in patients with breast cancer. Reported outcomes included overall survival, disease recurrences, bone metastases, distant metastases, visceral recurrences and local relapses.

The authors did not state how many reviewers undertook the selection process.

Assessment of study quality
The authors did not undertake a formal quality assessment, but they noted trial design items such as randomisation, allocation concealment and withdrawals.

Data extraction
Two authors independently extracted the number of events (deaths, disease recurrences and bone metastases) and used it to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Authors of included RCTs were unsuccessfully contacted for extra information.

Methods of synthesis
Pooled odds ratios, together with 95% CIs, were calculated using a fixed-effect or random-effects meta-analysis. Statistical heterogeneity was assessed using the X² statistic. Subgroup analyses were conducted according to type of bisphosphonate.

Results of the review
Thirteen RCTs were included in the review (n=6,886 patients): six trials of zoledronic acid; four trials of clodronate; two trials of pamidronate; and one trial of risendronate. Length of follow-up ranged from 12 to 120 months. Trial sample sizes ranged from 40 to 1,803 patients. All trials except one were based on intention-to-treat analysis. Nine trials
reported withdrawals. Three trials were double-blind. Three trials described the method of randomisation. Two trials reported allocation concealment. No significant statistical heterogeneity was observed in any analysis except number of deaths ($X^2 p=0.034$) and disease recurrences ($X^2 p=0.016$).

There was no statistical difference between bisphosphonates and control in terms of overall number of deaths (nine trials, $n=6,689$), disease recurrences (nine trials, $n=5,631$), bone metastases (eight trials, $n=5,571$), distant metastases (seven trials, $n=4,618$), visceral recurrences (four trials, $n=1,693$) and local relapses (five trials, $n=4,276$).

Subgroup analysis did not show any significant effect of any of the agents on death or bone metastases. Zoledronic acid showed a significantly lower risk of disease recurrence compared with control (OR 0.68, 95% CI 0.48 to 0.95; six trials, $n=4,142$).

**Authors' conclusions**

Available evidence did not support the hypothesis that bisphosphonates in the adjuvant treatment of early breast cancer will alter the natural course of disease.

**CRD commentary**

Inclusion criteria for the review were broadly defined. Several relevant databases were searched without language restrictions. Publication bias was not assessed and could not be ruled out. Two authors performed data extraction to minimise error and bias in the analysis; it was unclear whether study selection was undertaken in a similar manner. Quality assessment was not formally undertaken; details of trial design items indicated that some of the trials might not have been designed robustly. Baseline patient characteristics within the trials were not available, which made verifying the comparability of the included trials difficult. Trials were combined using meta-analysis, which, given the uncertain quality and comparability of trials, may not have been appropriate. Overall, some methodological weaknesses within the review limit the reliability of the authors' conclusions.

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

**Practice:** The authors stated that until further evidence was available, adjuvant bisphosphonates should not be recommended routinely.

**Research:** The authors stated that further randomised trials were needed before use of bisphosphonates in the adjuvant treatment of breast cancer could be definitely encouraged or discouraged. Results of ongoing phase III trials would be crucial for defining this.

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