Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a meta-analysis

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CRD summary

The authors concluded that jaw osteonecrosis was rare after adjuvant biphosphonate treatment in women with breast cancer. It was associated with biphosphonates (in particular zoledronic acid). Overall, biphosphonates were a safe adjuvant treatment. The review was generally well-conducted, but the conclusion that biphosphonates were safe may be optimistic given that zoledronic acid was associated with increased risk.

Authors' objectives

To estimate the overall incidence of bisphosphonate induced jaw osteonecrosis in the adjuvant treatment of breast cancer.

Searching

MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Knowledge were searched from inception to January 2009. No language restrictions were imposed. Search terms were reported. Abstracts from American Society of Clinical Oncology annual Meeting, San Antonio Breast Cancer Symposium, and European Cancer Conference were searched electronically. Reference lists of retrieved articles were searched.

Study selection

Randomised controlled trials (RCTs) that compared biphosphonates with placebo/no treatment in breast cancer patients in an adjuvant setting were eligible for inclusion. Studies had to provide data on osteonecrosis of the jaw. Non-randomised studies were excluded. Studies were also excluded if they did not state the number of patients with osteonecrosis of the jaw and authors were not able to provide this information when contacted. The included RCTs compared Zoledronic acid (4mg intravenously every three to six months), Ibandronate (150mg orally per month), Risedronate (35mg weekly), Clodronate (1,600mg orally per day) or Pamidronate (150mg orally twice daily) against no treatment/placebo in patients with breast cancer. Treatment regimes varied. Duration of treatment ranged from one to five years.

The authors did not state how many reviewers performed study selection.

Assessment of study quality

Validity was assessed using randomisation method, allocation concealment, withdrawals, blinding and performing of planned or unplanned interim analyses.

Two reviewers independently assessed validity and resolved disagreements through consensus with the aid of a third reviewer, if required.

Data extraction

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each study. Data extraction was conducted by two reviewers independently. Where disagreements occurred, consensus was achieved by consulting a third reviewer.

Methods of synthesis

The pooled odds ratios and 95% CIs were calculated using meta-analysis methodology for rare events. The Q statistic was used to assess heterogeneity. Sensitivity analysis was undertaken using different statistical methods to combine the data.

Results of the review

Fifteen RCTs (n=10,694) were included in the review. Length of follow-up ranged from six to 120 months. No
heterogeneity was found.

Zoledronic acid was evaluated in nine RCTs (n=7,990), clodronate in two RCTs (n=1,351), risedronate in two RCTs (n=350), pamidronate in one RCT (n=953) and ibandronate in one RCT (n=50). Four studies were double-blinded. Two studies reported method of randomisation and allocation concealment. Eight studies described withdrawals.

Osteonecrosis occurred in 13 out of 5,312 (0.24%) patients who received biphosphonates; all cases were in patients who received zoledronic acid (13 out of 3,987, 0.33%). In the control groups only one out of 5,382 patients developed osteonecrosis. The meta-analysis of zoledronic acid versus placebo/no treatment indicated that zoledronic acid was significantly associated with the occurrence of osteonecrosis of the jaw (OR 3.23, 95% CI 1.7 to 8) compared with control groups.

Sensitivity analysis with differing meta-analysis methodology found odds ratios that ranged from 3.23 to 13.6; all indicated that zoledronic acid was significantly associated with an increased risk of osteonecrosis of the jaw compared with no treatment.

Authors’ conclusions
Zoledronic acid was statistically associated with the development of jaw osteonecrosis compared with no therapy, but it was a very rare event. Overall, the authors considered biphosphonates (at current doses) to be a safe adjuvant therapy in breast cancer.

CRD commentary
This review addressed a well-defined question. Several relevant databases were searched. No language restrictions were imposed. However, there may have been potential for bias and error in the review as the authors did not appear to search for unpublished studies and may not have performed study selection in duplicate. Validity was assessed and results were reported. Pooling of data was undertaken using various statistical methods and heterogeneity was explored, all of which were appropriate. Overall, the review was well-conducted, but the conclusion that biphosphonates were safe may be optimistic given that zoledronic acid was associated with increased risk.

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

Research: The authors did not state any implications for research.

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