Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis

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CRD summary
This review found that treatment with bisphosphonates resulted in reductions in fractures and osteoporosis in patients under androgen-deprivation therapy for prostate cancer. A lack of information on study quality, some double-counting and omissions of some studies from the analysis mean that the reliability of the authors’ conclusions is unclear.

Authors’ objectives
To evaluate the effects of bisphosphonate therapy in patients with prostate cancer who were receiving androgen deprivation therapy.

Searching
MEDLINE, CancerLit, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to 2009 for relevant studies; search terms were reported. Abstracts from the proceedings of the Annual Meetings of the American Society of Clinical Oncology from 1998 to 2008 were checked for additional studies. References from review articles and cross-referenced studies from retrieved articles were screened for pertinent data.

Study selection
Eligible studies were randomised placebo-controlled trials that evaluated bisphosphonate therapy for treatment of bone loss in patients with prostate adenocarcinoma. Trials were required to report fracture incidence or data on bone mineral density. Studies of patients with other bone or mineral disorders were excluded from the review.

The patients presented with prostate cancer and some also presented with bone metastasis; a few presented with biochemical recurrence of cancer. The mean age of patients in both intervention and control groups ranged from 63 to 75.1 years. The bisphosphonate evaluated in most of the trials was zoledronic acid; other therapies assessed were pamidronate, alendronate, clodronate and neridronate. Where stated, control groups received calcium and vitamin D supplementation. Follow-up ranged from six to 36 months.

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

Assessment of study quality
The authors did not state that they assessed methodological quality.

Data extraction
Data on the main outcomes of fractures, skeletal-related events and adverse events were extracted to calculate risk ratios (RR) and 95% confidence intervals (CIs) for the estimates. The reviewers contacted study authors for additional information where required.

Three reviewers performed the data extraction; any discrepancies between the reviewers were resolved by consensus.

Methods of synthesis
Pooled risk ratios and 95% CIs for the summary were calculated using Mantel-Haenszel fixed-effect model. Numbers-needed to treat (NNT) for benefit were calculated. The presence of statistical heterogeneity was assessed using the $X^2$ test. Sensitivity analyses were conducted on the subgroups that differed by clinical features. The reviewers evaluated potential for publication bias by visual appraisals of funnel plots and with Begg and Egger tests.

Results of the review
Fifteen trials (2,634 participants, range 30 to 643) were included in the review.

There were statistically significant reductions in vertebral fractures in patients who received bisphosphonate therapy.
compared to placebo-treated patients (RR 0.80, 95% CI 0.69 to 0.94; I²=0%; seven trials; NNT=166.6). For the analysis by drug type, only zoledronic acid (three studies) was shown to be associated with significant reductions in fractures (RR 0.77, 95% CI 0.65 to 0.91; I²=21%; NNT=14.9).

Reductions in risk of osteoporosis were observed for patients who received bisphosphonate therapy compared to placebo (RR 0.39, 95% CI 0.28 to 0.55; I²=0%; four trials; NNT=2.82 patients). There was a significant reduction in risk of osteoporosis from zoledronic acid (RR 0.36, 95% CI 0.16 to 0.83; one trial; NNT=2.68 patients), alendronate (RR 0.44, 95% CI 0.29 to 0.67; I²=0%; two trials; NNT=3.06) and clodronate (RR 0.31, 95% CI 0.15 to 0.64; one trial; NNT 2.49).

Bisphosphonate-treated patients had increases in bone mineral density observed in the lumbar spine (5.18±3.38), total hip (2.56±0.89), trochanter (3.70±0.82) and femoral neck (2.35±1.16). Patients who received placebo had observed decreases in bone mineral density at all classes of evaluation.

Treatment with clodronate was significantly associated with higher risks of serious adverse effects (grade 3 to 4) compared to placebo (RR 2.72, 95% CI 1.71 to 4.31; one trial) and alendronate was associated with reduced risk of grade 3 to 4 adverse events (RR 0.60, 95% CI 0.40 to 0.88; I²=0%; two trials).

There were no significant differences between bisphosphonate-therapy groups and placebo-treated groups for cardiovascular events, cancer risk and gastrointestinal events. Zoledronic therapy was associated with significantly increased risks of musculoskeletal pain (RR 1.35, 95% CI 1.01 to 1.80; four trials), anaemia (RR 1.38, 95% CI 1.01 to 1.90; three trials), fatigue (RR 1.19, 95% CI 1.01 to 1.41; four trials) and fever (RR 1.67, 95% CI 1.15 to 2.43; three trials).

Visual appraisals of funnel plots and the results of Begg and Egger tests showed no evidence of publication bias.

**Authors' conclusions**

Treatment with bisphosphonate therapy resulted in significant reductions in fractures and osteoporosis in patients under androgen-deprivation therapy for prostate cancer.

**CRD commentary**

The review addressed a clear question. Criteria for inclusion of studies in the review were well-defined and reproducible. Appropriate databases were searched for relevant studies. Potential for publication bias was assessed using validated methods. Steps were taken to minimise errors and biases for data extraction but were not reported for study selection. Methodological quality of the included studies was not assessed and this made it difficult to assess the reliability of the results.

The authors’ decision to combine the results in a meta-analysis appeared justified given the lack of statistical heterogeneity observed in the results but few of the included studies were included in the meta-analysis. Results from some studies were counted twice in the meta-analysis and the review.

A lack of information on the methodological quality of the included studies and the double-counting of some of the results means that the reliability of the authors' conclusions is not clear.

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

**Practice:** The authors stated that standard treatment of cancer treatment induced bone loss in patients with prostate cancer should include bisphosphonates. Zoledronic acid should be administered as first-line treatment; second-line options included pamidronate and alendronate.

**Research:** The authors stated that bisphosphonate therapy should be compared to selective oestrogen receptor modulators and denosumab (a monoclonal antibody against the RANK ligand) to determine effects on bone mineral density.

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