The use of bisphosphonates in men with hormone-refractory prostate cancer
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CRD summary
This review concluded that bisphosphonates may reduce bone pain in hormone-refractory prostate cancer, but the evidence was not so robust. Although some details of the review methodology were not reported, this conclusion appears reliable. The authors appropriately identified the need for further research to clarify improvements in pain in subsets of patients and in observed trends.

Authors' objectives
To determine the benefits of bisphosphonates in men with hormone-refractory prostate cancer (HRPC).

Searching
MEDLINE (1980 to July 2004), EMBASE (1980 to week 32, 2004), Cancerlit (1980 to October 2002) and the Cochrane Library (Issue 2, 2004) were searched. Some details of the search strategy were reported. Conference proceedings of the American Society of Clinical Oncology (1995 to 2004) and the American Urological Association (1995 to 2004) were also searched. The reference lists from these sources and from relevant review articles were also checked.

Study selection
Study designs of evaluations included in the review
To be eligible, studies needed to be randomised controlled trials (RCTs). Systematic reviews were used as a source of eligible trials.

Specific interventions included in the review
To be eligible, studies needed to compare treatment with a bisphosphonate with placebo or no treatment, or compare different bisphosphonates or routes of administration of the same bisphosphonate, or compare treatment with a bisphosphonate plus a cointervention with bisphosphonate alone. The trials studied clodronate, pamidronate, alendronate, etidronate or zoledronic acid. Where stated, treatment lasted between 2 weeks and 15 months.

Participants included in the review
To be eligible, studies needed to be of men with HRPC. Most of the included studies were in men with bone metastases and pain; in one study men had bone metastases but no pain at baseline.

Outcomes assessed in the review
To be eligible, studies needed to report at least one of the following outcomes: incidence of new bone metastases, skeletal-related events (SREs), palliative or symptom response rates, survival and/or quality of life. Adverse effects were also included. The included studies used different methods to measure pain.

How were decisions on the relevance of primary studies made?
Three reviewers selected articles for the review.

Assessment of study quality
The quality assessment focused on methods of randomisation and blinding, adequacy of description of treatment and control arms, completeness of follow-up and whether intention-to-treat analyses were performed. It is not clear how many reviewers were involved in the quality assessment.

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

Methods of synthesis
How were the studies combined?
The studies were grouped by outcome and combined in a narrative.

How were differences between studies investigated?
Differences between the studies were explored within the text.

Results of the review

Ten RCTs (1,497 patients) were included in the review. The sample size ranged from 13 to 643.

Nine trials were placebo-controlled, of which seven described double-blinding. Two trials described randomisation methods. Four trials estimated sample size and described study power. Two trials performed analysis according to intention-to-treat. Patient follow-up and details of those who had completed treatment as per protocol or had withdrawn were rarely reported.

Four of five clodronate trials did not detect significant differences in pain outcomes between clodronate and placebo. The fifth had some methodological problems (including having just 2 weeks’ follow-up of 13 patients). No statistically significant differences in mean pain scores were detected between treatment arms at 9 and 27 weeks in a pooled analysis of two pamidronate trials. Statistically significantly lower increases in pain scores were observed when comparing zoledronic acid with placebo in the only trial to investigate this.

The trial investigating zoledronic acid found a statistically significant reduction in the number of patients having at least one SRE after 15 months and 24 months of treatment at a dose of 4 mg. The pamidronate trials found no difference in rates of SRE. Other trials did not report this outcome.

None of three trials investigating survival detected a statistically significant difference between treatment groups (two trials of clodronate and one of zoledronic acid).

Two trials investigated quality of life. One of zoledronic acid found no statistically significant difference between groups and one of clodronate found improvements compared with placebo only in the pain domain.

Overall, bisphosphonates were well tolerated with the majority of trials finding similar proportions of mild toxicity between bisphosphonate and placebo. Greater proportions of adverse events in comparison with placebo were observed in the zoledronic acid trial.

Authors’ conclusions

The benefits of zoledronic acid in terms of reductions in SREs in patients with HRPC should be weighed against the associated toxicities and the lack of an effect on quality of life. Bisphosphonates may reduce bone pain in men with HRPC, but the evidence is less robust.

CRD commentary

Inclusion criteria were stated for the study design, participants, interventions and outcomes. The searches encompassed several databases and other sources. The quality of the studies was assessed and quality issues were used to interpret the study results. The narrative synthesis appears appropriate given the diversity of the treatments and regimens. Although some details of the review methodology were not reported (e.g. the number of reviewers involved in each stage of the review), the authors’ conclusions took account of study quality and appear reliable. The authors carefully considered both treatment benefits and risks, and appropriately identified the need for further research to clarify improvements in pain seen in subsets of patients and in trends observed.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further investigations to identify the role of bisphosphonates alone and in combination with other treatments in men with HRPC are warranted.
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Other publications of related interest


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Record Status
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.