Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers: an evidence-based review

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Authors' objectives
To review the evidence for the use of bisphosphonates for the reduction of skeletal events, or for the management of pain due to multiple myeloma or to bone metastases from other types of cancer.

Searching
MEDLINE was searched from 1976 onwards using the keywords 'exp diphosphonates/' and 'exp bone neoplasms/' or 'exp multiple myeloma/' or 'bone metastases' as textwords.

Methodologic terms were specifically excluded from the search. Additional studies were identified by examining current issues of journals specific to cancer research and bibliographies of retrieved papers, and by contacting experts in the field.

Study selection
Study designs of evaluations included in the review
The trials considered were either Level I trials, i.e. large randomised trials with clear cut results and a low risk of error, or Level II trials, i.e. small randomised trials with uncertain results and a moderate to high risk of error.

Specific interventions included in the review
The specific interventions for bone metastases originating from breast cancer were oral administration of pamidronate (300 mg/day), intravenous (i.v.) administration of pamidronate (45 mg taken 3 times a week, or 90 mg taken 3 to 4 times a week), and oral administration of clodronate (1.6 g/day). For bone metastases originating from multiple myelomas, the treatments were etidronate (5 mg/kg per day, oral administration), clodronate (2.4 g/day, oral administration) and pamidronate (90 mg taken 4 times a week, i.v. administration).

Participants included in the review
The participants were patients with myeloma or bone metastases from solid tumors, treated with a bisphosphonate.

Outcomes assessed in the review
The primary outcomes assessed in the review were reduction in bone pain or skeletal events, and quality of life. The secondary outcomes were survival and adverse effects from treatment.

The reduction in pain was measured as a statistically-significant reduction in either a self-assessed pain scale or in pain analgesia. Quality of life was measured by a validated instrument where possible. The evidence for a reduction in skeletal events included radiologic assessment of lytic lesions or fractures; a reduction in clinical pathologic fractures; and a reduction in the need-to-treat bone pain, or impending fracture, by radiation or surgery.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
No formal assessment of quality was made, although the trials were graded at inclusion into level I and level II categories of evidence.

Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

**Methods of synthesis**

How were the studies combined?
The studies were discussed in a narrative review. There was no statistical combination of the individual study results. The included studies were reviewed for data relating to the three primary outcomes (reduction of skeletal events, pain reduction and quality of life) and the two secondary outcomes (survival and adverse events in treatment).

How were differences between studies investigated?
The author does not state how differences between the studies were investigated.

**Results of the review**
The author stated that 18 studies were included; however there is confusion since studies excluded during the review might have been included in this total.

Three randomised controlled trials (RCTs) examined multiple myelomas (908 participants), 6 RCTs examined the use of bisphosphonates in breast cancer (1,312 participants), 2 RCTs examined the use of bisphosphonates in prostate cancer (156 participants), 3 RCTs examined the use of bisphosphonates for the management of bone pain due to metastatic cancer (79 participants), and 3 further papers (study design not noted) examined adverse events associated with the use of bisphosphonates.

For multiple myeloma, there was level I evidence (1 trial, 392 participants) that i.v. pamidronate in conjunction with standard chemotherapy would result in a significant reduction in skeletal events and pain. There was also level I evidence (1 trial, 350 participants) that oral clodronate could reduce radiologic lytic lesions.

For breast cancer, there was level I evidence that clodronate or pamidronate could significantly reduce skeletal events (4 trials, 1,055 participants) and pain (3 trials, 882 participants) once bone metastases were present.

In prostate cancer, there was level II evidence (2 studies, 156 participants) that there was no benefit from oral clodronate in either skeletal events or pain reduction.

For bony metastatic disease, there was level I evidence (2 trials, 79 participants) supporting the use of pamidronate and clodronate as part of a pain-management programme.

There was evidence against the use of etidronate for bony metastatic disease. None of the reviews reported major toxicity, however there were rare instances of adverse ocular events associated with bisphosphonates.

**Authors’ conclusions**
At present, there is sufficient evidence to propose practice guidelines that would include the use of bisphosphonates in the management of multiple myeloma and breast cancer with bone metastases.

**CRD commentary**
The author conducted a competent narrative review of the literature. The author searched for articles using MEDLINE, and examined cancer research journals and the reference lists of retrieved articles for additional studies. The search was restricted to English language publications, and so, relevant studies published in other languages could have been missed. The author also contacted researchers in the field to identify further studies.

The inclusion criteria were stated but there was no discussion of how judgements were made about the relevance of the included studies. The author did not assess the quality of the included studies although they graded them into two levels of evidence; however, the criteria for this selection were poor. The review did not describe the criteria or methods for the data extraction.
The results of the review should be viewed with caution because of limitations in the literature search, and the lack of a detailed quality assessment of selected articles.

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

The author states that further RCTs should be conducted to assess the economic impact of using bisphosphonates on a widespread basis. It is also stated that the use of bisphosphonates in the treatment of prostate cancer requires further clinical investigation, and that practice guidelines for the use of bisphosphonates need to be developed.

**Bibliographic details**

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