

Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer

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Abstract

Objective To review the evidence for the use of bisphosphonates to reduce skeletal morbidity in cancer patients with bone metastases.

Data sources Electronic databases, scanning reference lists, and consultation with experts and pharmaceutical companies. Foreign language papers were included.

Study selection Included trials were randomised controlled trials of patients with malignant disease and bone metastases who were treated with oral or intravenous bisphosphonate compared with another bisphosphonate, placebo, or standard care. All trials measured at least one outcome of skeletal morbidity.

Results 95 articles were identified; 30 studies fulfilled inclusion criteria. In studies that lasted ≥ 6 months, compared with placebo bisphosphonates significantly reduced the odds ratio for fractures (vertebral 0.69, 95% confidence interval 0.57 to 0.84, $P < 0.0001$; non-vertebral 0.65, 0.54 to 0.79, $P < 0.0001$; combined 0.65, 0.55 to 0.78, $P < 0.0001$), radiotherapy (0.67, 0.57 to 0.79, $P < 0.0001$), and hypercalcaemia (0.54, 0.36 to 0.81, $P = 0.003$) but not for orthopaedic surgery (0.70, 0.46 to 1.05, $P = 0.086$) or spinal cord compression (0.71, 0.47 to 1.08, $P = 0.113$). The reduction in orthopaedic surgery was significant in studies that lasted over a year (0.59, 0.39 to 0.88, $P = 0.009$). Use of bisphosphonates significantly increased time to first skeletal related event but did not increase survival. Subanalyses showed that most evidence supports use of intravenous aminobisphosphonates.

Conclusions In people with metastatic bone disease bisphosphonates significantly decrease skeletal morbidity, except for spinal cord compression and increased time to first skeletal related event. Treatment should start when bone metastases are diagnosed and continue until it is no longer clinically relevant.

Introduction

Metastatic bone disease causes substantial morbidity among cancer patients. Complications from bone metastases include pathological fracture, hypercalcaemia, nerve root compression, spinal cord compression, bone marrow infiltration, pain, and reduced mobility.^{1,2} Although there are many therapeutic options for the treatment of such complications, none is completely satisfactory, even when used in combination. These

patients continue to represent a major therapeutic challenge for the clinician.

Bisphosphonates work by several different mechanisms to reduce both bone resorption and bone formation.^{3,4} In vitro work has shown that bisphosphonates may have a direct action on tumour cells—for example, by inducing apoptosis, inhibiting matrix metalloproteinase-1, and inhibiting adhesion of tumour cells within the bone.⁵ Bisphosphonates can be divided into two groups. Those resembling pyrophosphate (for example, clodronate, etidronate) act as analogues of ATP and inhibit ATP dependent intracellular enzymes. The second group—aminobisphosphonates (for example, pamidronate, zoledronic acid)—inhibit enzymes of the mevalonate pathway, disrupting the signalling functions of key regulatory proteins.⁶⁻⁹ The net effect in both groups is inhibition of osteoclast function, which leads to a decrease in bone resorption.

We have assessed the evidence for the role of bisphosphonates in the reduction of skeletal morbidity in patients with bone metastases. We looked at who would benefit from treatment, when treatment should be started, and for how long it should be continued. We also compared different drugs, routes of administration, and tolerability.

Methods

Inclusion criteria—We included randomised controlled trials of patients with proved malignant disease and bone metastases. We included patients with multiple myeloma but excluded other haematological malignancies.

Outcome measures—Our primary outcome measures were time to first skeletal related event and reduction in skeletal morbidity assessed by pathological fractures (vertebral, non-vertebral, combined), radiotherapy to bone metastases, spinal cord compression, orthopaedic surgery, and hypercalcaemia. We did not include pain relief as an end point.¹⁰ Secondary analyses determined the efficacy of bisphosphonates over time, the efficacy of one bisphosphonate over another, and the effect in different disease groups, specifically breast cancer and multiple myeloma, and compared routes of administration.

Identification of studies—We identified studies by searching electronic databases (see bmj.com), scanning reference lists of articles, and consulting experts in the specialty and drug companies for unpublished data.

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BMJ 2003;327:469-72



Two tables of the included and excluded trials and a full list of references (w1-w98) can also be found on bmj.com

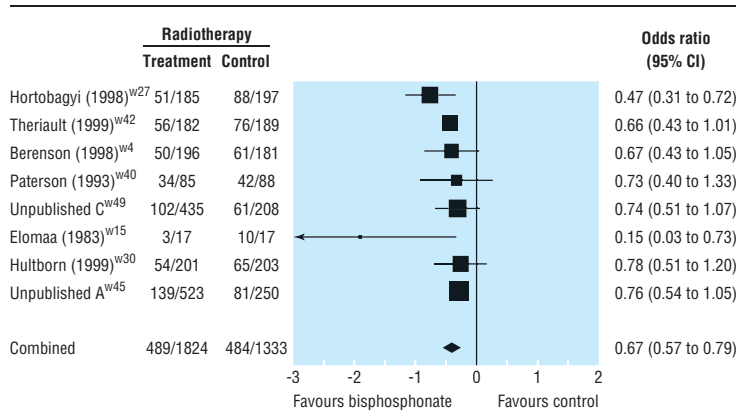


Fig 1 Forest plot for radiotherapy (3140 patients)

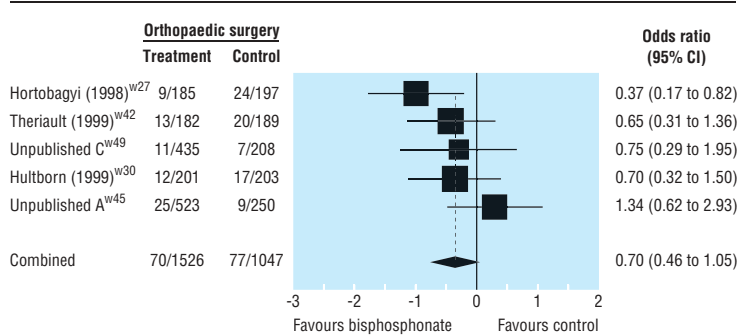


Fig 2 Forest plot for orthopaedic surgery (2556 patients)

The last search was run on 19 June 2001. In addition, we hand searched *Journal of Clinical Oncology* 2001, *European Journal of Cancer* 2001, and *Bone* 2001 and meeting abstracts (1999-2001). All randomised controlled trials were assessed and graded for allocation concealment and blinding.

Summary statistics from pooled analysis at fixed time points for effect of bisphosphonates on radiotherapy, non-vertebral fractures, orthopaedic surgery, and hypercalcaemia in patients with metastatic bone disease

Months of treatment	No of studies	No of patients	Odds ratio (95% CI)	P value
Radiotherapy				
6-11	4	1903	0.60 (0.47 to 0.77)	0.0001
12-17	5	1807	0.54 (0.38 to 0.76)	0.0001
18-23	3	1130	0.58 (0.44 to 0.76)	0.0001
≥24	2	753	0.56 (0.40 to 0.78)	0.001
Non-vertebral fractures				
6-11	4	1903	0.75 (0.50 to 1.14)	0.179
12-17	4	1430	0.68 (0.48 to 0.96)	0.031
18-23	2	753	0.68 (0.41 to 1.12)	0.129
≥24	2	753	0.65 (0.37 to 1.14)	0.132
Orthopaedic surgery				
6-11	3	1526	0.92 (0.36 to 2.35)	0.866
12-17	3	1396	0.61 (0.37 to 1.01)	0.054
18-23	2	753	0.52 (0.26 to 1.05)	0.067
≥24	2	753	0.49 (0.28 to 0.86)	0.013
Hypercalcaemia				
6-11	5	1916	0.42 (0.24 to 0.74)	0.003
12-17	5	1807	0.50 (0.28 to 0.90)	0.02
18-23	3	1130	0.56 (0.27 to 1.17)	0.12
≥24	2	753	0.42 (0.34 to 0.51)	0.0001

Data synthesis—We weighted studies with the inverse variance method and applied a random effects model to all meta-analyses.

Results

Forty seven papers describing 30 studies fulfilled the inclusion criteria for this review. Data extracted from 18 studies were eligible for inclusion in the meta-analyses. The meta-analysis also included three large trials of zoledronic acid, which were unpublished at the time of inclusion in this review. We are aware of further unpublished trials of ibandronic acid but were not able to include the data in this review. Details of all trials can be found on bmj.com (tables A and B).

Primary end points

Compared with placebo, bisphosphonates significantly reduced the odds ratio for vertebral fractures (0.69, 95% confidence interval 0.57 to 0.84, 3238 patients), non-vertebral fractures (0.65, 0.54 to 0.79, 3376 patients), combined fractures (0.65, 0.55 to 0.78, 2587 patients), radiotherapy (0.67, 0.57 to 0.79, fig 1), and hypercalcaemia (0.54, 0.36 to 0.81, 3894 patients) but not orthopaedic surgery (0.70, 0.46 to 1.05, fig 2) or spinal cord compression (0.71, 0.47 to 1.08, 2628 patients). The risk of an individual skeletal related event for those taking bisphosphonates was 65% of the risk in patients not taking bisphosphonates for non-vertebral fractures, 69% for vertebral fractures, 67% for radiotherapy, and 54% for hypercalcaemia.

Ten studies included in the analyses recorded time to first skeletal related event for patients treated with bisphosphonate versus control (see bmj.com). We could not statistically combine the data. Eight studies showed a significant increase in time to first event for patients who received bisphosphonate: four used intravenous pamidronate, two used intravenous zoledronic acid, and two used oral clodronate. In contrast, two studies that used oral clodronate did not show a significant difference in time to first event. One study that compared zoledronic acid with pamidronate showed no difference in time to first event between the two drugs.

Secondary end points

Time—Reduction in the need for radiotherapy was significant at six months, episodes of hypercalcaemia at six months, and non-vertebral fractures at 12 months. The need for orthopaedic surgery progressively decreased with narrowing of the confidence interval over time, reaching significance at 24 months. Studies of less than six months' duration did not show significant results for any skeletal morbidity outcome (table).

Disease groups—In the five trials among patients with breast cancer, compared with placebo bisphosphonates significantly reduced the odds ratio for non-vertebral fractures (0.80, 0.64 to 0.99), combined fractures (0.75, 0.61 to 0.93), radiotherapy (0.65, 0.54 to 0.79), orthopaedic surgery (0.59, 0.43 to 0.83), and hypercalcaemia (0.43, 0.29 to 0.63) but not spinal cord compression (0.87, 0.44 to 1.73) or vertebral fractures (0.87, 0.71 to 1.06). By contrast, in the three trials among patients with multiple myeloma, the odds ratios were significantly reduced for vertebral fractures (0.58, 0.42 to 0.81) but not for hypercalcaemia (0.97, 0.69 to

1.37). In one trial that studied patients with prostate cancer the odds ratio was significantly reduced for combined fractures (0.57, 0.38 to 0.89). Two trials included patients with various cancer diagnoses.

Route of administration—Six trials studied intravenous bisphosphonates. Results were similar to those from the primary analysis (see bmj.com). Treatment with oral bisphosphonates (five trials) significantly reduced the odds ratio for vertebral and non-vertebral fractures. The reduction in radiotherapy was not significant, but only 193 patients contributed to this analysis. The reduction in hypercalcaemia was also not significant, but this analysis was weighted by one study in patients with myeloma, which contributed over half of the 1064 patients.

Survival and toxicity—None of the individual studies found a significant difference in survival between patients treated with bisphosphonates and controls. All bisphosphonates were well tolerated. Generally oral medications were associated with increased incidence of gastrointestinal side effects, but these were often reflected in placebo groups. Aminobisphosphonates were associated with a higher proportion of acute phase reactions.

Discussion

This systematic review supports the use of bisphosphonates to reduce skeletal morbidity in cancer patients with metastatic bone disease. Though some evidence based guidelines have been developed,^{11 12} clinical practice varies between centres. We have provided some answers relating to the clinical use of bisphosphonates.

Limitations

We were unable to include results of all of the studies in the meta-analyses because of differences in the way results were reported. Our attempts to contact all authors for raw data were rarely successful.

Interpretation from available evidence

Bisphosphonates reduce skeletal morbidity in cancer patients with metastatic bone disease. The primary analyses show a highly significant reduction in fractures, need for radiotherapy, and hypercalcaemia in patients receiving bisphosphonates. The reduction in need for orthopaedic surgery became significant with time, the odds ratio being 0.59 (0.40 to 0.88, $P < 0.009$) for studies that lasted at least 12 months. There was no reduction in the incidence of spinal cord compression.

Most of the trials of bisphosphonates have been performed in patients with breast cancer and multiple myeloma. The increased reduction in vertebral fractures in patients with myeloma compared with patients with breast cancer may be explained by more active disease in the vertebrae in myeloma patients. Lack of reduction in hypercalcaemia in patients with myeloma was surprising but may reflect mechanisms other than action of parathyroid hormone related protein and cytokines¹³; in particular renal handling of calcium may be impaired.^{13 14} Two recently released Cochrane reviews have looked at these disease groups, and their results are consistent with our findings.^{15 16}

Regarding other disease groups, one study in patients with prostate cancer showed a significant reduction in combined fractures and a trend towards a reduc-

tion in radiotherapy. This study did not last long enough to show a reduction in orthopaedic surgery. Preliminary results from another study in patients with prostate cancer also indicated that treatment delays the development of skeletal morbidity.¹⁷ The case is less clear for patients with other solid tumours, particularly those that have shorter prognoses (less than six months).

Most patients in clinical trials had osteolytic bone metastases on imaging studies. Recent guidelines from the American Society for Clinical Oncology (ASCO) for management of breast cancer recommend the use of bisphosphonates if there is lytic bone destruction.¹¹ They note that there is insufficient evidence to recommend bisphosphonates for asymptomatic patients with an abnormal result on a bone scan. However, our results suggest that bisphosphonates should be started at diagnosis of bone metastases as time to first skeletal related event can be significantly delayed. This delay is likely to result in cost savings for the NHS.¹⁸ While it is also probable that patients' quality of life will be improved by early treatment and subsequent delay in time to skeletal morbidity, there are few data on quality of life from existing trials to support this premise.

Clinical inferences

Our findings show that bisphosphonates need to be given for at least six months before an effect is seen on skeletal morbidity outcomes. Studies that lasted less than six months did not show a reduction in skeletal related events, although this may reflect the small numbers and low event rates in these studies. In addition, a reduction in orthopaedic surgery was not seen until 12-24 months. The ASCO guidelines for breast cancer accept that the optimal duration of bisphosphonate therapy is unknown. Initial benefits may not be maintained once the drug is discontinued.¹⁹ We recommend that bisphosphonates are continued until no longer clinically relevant. This is supported by ASCO guidelines.¹¹

It was difficult to separate the effect of the drug from the route of administration as the aminobisphospho-

What is already known on this topic

Individual studies have shown that patients with breast cancer who receive bisphosphonates to treat skeletal morbidity may experience a benefit

The magnitude of benefit, who to treat, when to treat, and for how long remains unclear

What this study adds

For patients with cancer and bone metastases, pooled results show that treatment with bisphosphonates is associated with a significant reduction in all skeletal morbidity end points except spinal cord compression

Bisphosphonates significantly increase the time to first skeletal related event, suggesting they should be started when bone metastases are diagnosed

Bisphosphonates reduce skeletal morbidity and should be continued until no longer clinically relevant; they do not affect survival

Most evidence supports the use of intravenous aminobisphosphonates, but further studies are needed to determine best drug and route

nates pamidronate and zoledronic acid are given intravenously whereas the principal oral agent was the non-aminobisphosphonate clodronate (see also bmj.com). Intravenous bisphosphonates have better bioavailability than oral bisphosphonates.^{20 21} The pooled results of trials that used intravenous bisphosphonates were highly significant and mirror the primary analysis. In comparison, oral bisphosphonates showed a significant reduction in only vertebral and non-vertebral fractures, but numbers contributing to the analysis were small. Therefore, at present, most evidence supports the use of intravenous aminobisphosphonates.

Further research is needed to determine the optimum regimen required to treat patients with bone metastases. Clinical trials of bisphosphonates in other disease groups are needed.

We thank members of the project steering group (R A'Hern, R Chinn, D Dearnaley, M Dowsett, S Evans, D Feuer, J Hardy, C Normand, T Powles, D Wonderling) for their guidance. We are grateful to various authors and Novartis Pharmaceuticals who contributed unpublished data.

Contributors: See bmj.com

Funding: This review was funded by the NHS Health and Technology Assessment Programme. The conclusions do not necessarily reflect the views of the funding body. The guarantor accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

Competing interests: None declared.

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(Accepted 9 July 2003)



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BMJ 2003;327:472-5

Child psychiatric disorder and relative age within school year: cross sectional survey of large population sample

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Abstract

Objective To test the hypothesis that younger children in a school year are at greater risk of emotional and behavioural problems.

Design Cross sectional survey.

Setting Community sample from England, Scotland, and Wales.

Participants 10 438 British 5-15 year olds.

Main outcome measures Total symptom scores on psychopathology questionnaires completed by parents, teachers, and 11-15 year olds; psychiatric diagnoses based on a clinical review of detailed interview data.

Results Younger children in a school year were significantly more likely to have higher symptom scores and psychiatric disorder. The adjusted regression coefficients for relative age were 0.51 (95%

confidence interval 0.36 to 0.65, $P < 0.0001$) according to teacher report and 0.35 (0.23 to 0.47, $P = 0.0001$) for parental report. The adjusted odds ratio for psychiatric diagnoses for decreasing relative age was 1.14 (1.03 to 1.25, $P = 0.009$). The effect was evident across different measures, raters, and age bands. Cross national comparisons supported a "relative age" explanation based on the disadvantages of immaturity rather than a "season of birth" explanation based on seasonal variation in biological risk.

Conclusions The younger children in a school year are at slightly greater psychiatric risk than older children. Increased awareness by teachers of the relative age of their pupils and a more flexible approach to children's progression through school might reduce the number of children with impairing psychiatric disorders in the general population.