Clinical review

Recent developments in bisphosphonates for patients with metastatic breast cancer

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Breast cancer is the most common malignancy in women in North America. In 2004 there have been an estimated 215 990 new cases and 40 110 deaths.[1] Unfortunately, despite adjuvant treatment, 24-60% of women will ultimately develop metastatic disease. Bone remains the most common site of distant recurrence of disease and is affected in an estimated 65-75% of women with advanced breast cancer. Of those women with bone metastases, two thirds will subsequently develop skeletal related events (box).

Bisphosphonates are an established standard of care for patients with bone metastases, and although they have been shown to have some analgesic effect, the major indication for their use is to reduce the incidence and delay the onset of subsequent skeletal related events. Despite their rapid integration into standard clinical practice many uncertainties remain with regard to their use. We review the limitations of current bisphosphonate studies and the implications these have for patients in clinical practice and direct healthcare costs.

Recent developments

- Bisphosphonates are an established standard of care for breast cancer patients with bone metastases
- Randomised controlled trials confirm significant reductions in skeletal related events with bisphosphonates
- Bisphosphonate effects are time dependent; benefits in terms of skeletal related events begin to be identified after six months of treatment
- Bisphosphonates work best in those patients with bone only disease—namely, those who live long enough to gain benefit
- Previous trials contained highly selected patient populations who were most likely to benefit from treatment with bisphosphonates
- The benefits of bisphosphonates in patients with a poor prognosis, the optimal duration of treatment, and the optimal bisphosphonate remain unknown

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BMJ 2005;330:769–73

Methods

We searched the PubMed database to identify data for this review. We used a combination of the terms "breast cancer, bone metastases, bisphosphonates" and identified the reference lists of publications. We used articles published only up to January 2005. We also identified relevant abstracts from the proceedings of major oncology conferences in 2002, 2003, and 2004.

Bisphosphonate studies

The bisphosphonates are inhibitors of osteoclast mediated bone resorption. Randomised trials comparing bisphosphonates with either a placebo or no treatment in secondary prophylaxis (in patients with breast cancer and established bone metastases) have shown that once bone metastases are present, bisphosphonates in addition to chemotherapy or hormonal therapy can significantly reduce skeletal related events (tables 1 and 2).[2–13]

A recent systematic review by Ross confirmed the beneficial effects of bisphosphonates.[14] In the five trials among patients with breast cancer, bisphosphonates were compared with either placebo or no bisphosphonate and were found to reduce significantly the risk of non-vertebral fractures (odds ratio 0.80, 95% confidence interval 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).

A systematic review by Pavlakis and Stockler (this is among studies of intravenous pamidronate and oral bisphosphonates) has shown that 90 mg intravenous pamidronate is the most effective agent to reduce the risk of developing a skeletal related event (relative risk 0.77, 95% confidence interval 0.69 to 0.87), being more effective than pamidronate 45 mg (0.97, 0.79 to 1.19), 60 mg (0.97, 0.87 to 1.07) or oral bisphosphonates (pooled relative risk 0.83, 0.73 to 0.94).[15]

Results from a study comparing intravenous pamidronate 90 mg with intravenous zolendronic acid 4 mg or 8 mg has shown equivalent efficacy for these two agents in all patients with bone metastases from

Definition of skeletal related events

Generally includes
Pathological vertebral fractures
Pathological non-vertebral fractures
Spinal cord compression
Surgery for bone complications
Radiotherapy for bone complications
Hypercalcaemia

Does not include
Pain
Immobility
Analgesic use
Non-hospital costs (physiotherapy)

breast cancer.[16] The proportion of patients who had a skeletal related event—the primary end point of the study—was comparable between treatment groups (43% for zolendronic acid 4 mg and 45% for pamidronate). However, in the subgroup of breast cancer patients with lytic metastases, zolendronic acid showed a significant clinical benefit compared with pamidronate in several secondary end points; prolonged time to first skeletal related event (310 days *v* 174 days, P = 0.013), and reduced annual incidence of skeletal events (mean 1.2 *v* 2.4 events per year, P = 0.008). Subsequent, multiple events analysis found significant further reductions in the risk of developing skeletal related events over the reduction achieved with pamidronate; 20% for all patients with breast cancer (P = 0.037) and 30% in the osteolytic subset (P = 0.010). Interestingly, two of the randomised trials of bisphosphonates compared with placebo were restricted to patients with predominantly lytic metastases.[5 6]

With regard to the analgesic properties of the bisphosphonates, their role is less clear. A systematic review by Wong and Wiffen to determine the effectiveness of bisphosphonates for the relief of pain from bone metastases concluded that there was evidence to support their effectiveness in providing some pain relief.[17] Evidence was, however, insufficient to recommend their use as first line therapy or to define the most effective bisphosphonate or the relative effectiveness of biphosphonates for different primary neoplasms. This uncertainty regarding the analgesic benefits of bisphosphonates is reflected in the conflicting results reported in trials including breast cancer patients.

A combined analysis of two studies of pamidronate confirmed that fewer patients in the pamidronate group (40% *v* 52%, P = 0.003) experienced an increase in pain during the study.[3] Although the mean pain scores and analgesic scores at the last visit increased in both groups, they increased significantly less in the pamidronate group than in the placebo arm (P < 0.001). Treatment with a bisphosphonate significantly reduced the need for radiotherapy to the bone for pain relief during the study (25% *v* 37%; P < 0.001).

However, other trials of intravenous pamidronate have been inconclusive or have had negative results in relation to pain control.[4 7] Similar conflicting results have been reported in trials of oral clodronate.[15] Ibandronate, in oral and intravenous form, has been shown to reduce bone pain scores.[2 8] With intravenous ibandronate, 6 mg produced a significantly improved bone pain score over time compared with placebo and ibandronate 2 mg. With oral ibandronate, the mean analgesic score was higher in the placebo group than for either active treatment group, with significance reached in the 20 mg group (P = 0.006 *v* placebo).

The role of bisphosphonates in the primary prevention of bone metastases in women with breast cancer has been widely explored and may prove in the future to be one of the most exciting uses of these agents. However, this role is still being investigated extensively.[18]

Statistical considerations

The primary outcome measures for many of the randomised studies has been the skeletal morbidity rate and the skeletal morbidity period rate. Bony complications are, however, an example of how multiple adverse events of a similar type can occur in the same individual. The occurrence of the first adverse event does not preclude a future benefit of the treatment, and the magnitude of this benefit is unknown. Therefore, the total number and type of bony complications, in addition to prevention, are relevant when assessing the benefit of bisphosphonate therapy. When evaluating the impact of bisphosphonates, appropriate

Table 1 Studies of intravenous bisphosphonate compared with placebo or no treatment

Bisphosphonate	No of patients	Eligibility criteria	% of patients with bone only disease enrolled in study	Primary end point	Results (P value of difference from placebo)
Ibandronate[2]	466	Life expectancy >60 weeks	66-69%	Skeletal morbidity period rate*	Ibandronate 6 mg: 1.19 (0.004) Ibandronate 2 mg: 1.31 (0.152) Placebo: 1.48
Pamidronate[3]	754	Life expectancy >9 months	64-66%	Skeletal morbidity rate† (+hypercalcaemia of malignancy)	Pamidronate 90 mg: 2.5 (<0.001) Placebo: 4.0
Pamidronate[4]	404	Life expectancy at least 3 months	54-57%	Cumulative skeletal symptom events	Pamidronate 60 mg: 200 (0.0042) Placebo: 278
Pamidronate[5]	372	Life expectancy at least 9 months	66-72%	Skeletal morbidity rate	Pamidronate 90 mg: 2.4 (0.008) Placebo: 3.8
Pamidronate[6]	382	Life expectancy at least 9 months	60-62%	Proportion of patients in whom any skeletal related event occurred	Pamidronate 90 mg: 43% (0.008) Placebo: 56%
Pamidronate[7]	295	N/A	52-58%	Progression of disease in bone (days)	Pamidronate45 mg: 249 (0.02) No bisphosphonate: 168
				Marked pain reduction (%)	Pamidronate 45mg: 44% (0.025) No bisphosphonate: 30%

N/A=Not available.
*Number of 12 week periods with new skeletal complications divided by the number of periods on study.
†Ratio of the number of skeletal complications experienced by a patient divided by the time on the trial by the end of the specified time period.

Table 2 Studies of oral bisphosphonate compared with placebo or no treatment

Bisphosphonate	No of patients	Eligibility criteria	% of patients with bone only disease enrolled in study	Primary end point	Results (P value of difference from placebo or control)
Ibandronate[8]	435	Life expectancy >60 weeks	N/A	Skeletal morbidity period rate*	Ibandronate 20 mg: 0.97 (0.024) Ibandronate 50 mg: 0.98 (0.037) Placebo: 1.20
Ibandronate[9]	564	Life expectancy >60 weeks	N/A	Skeletal morbidity period rate	Ibandronate 50 mg: 0.99 (0.041) Placebo: 1.15
Clodronate[10]	144	N/A	N/A	Time to new bone event (days)	Clodronate 1600 mg: 244 (0.05) Placebo: 180
Clodronate[11]	100	Life expectancy >6 months	N/A	No of skeletal related events	Clodronate 1600 mg: 14/49 (N/A) Control: 21/51
Clodronate[12]	173	N/A	18-32%	Mean skeletal morbidity rate†	Clodronate 1600 mg: 218.6 (<0.001) Placebo: 304.8
Pamidronate[13]	161	Life expectancy >6 months	N/A	Total No of complications	Pamidronate 300 mg: 90 (0.003) Control: 144
				Mean No of complications	Pamidronate 300 mg: 6.1 (0.02) Control: 8.1

N/A: Not available.
*Number of 12 week periods with new skeletal complications divided by the number of periods on study.
†Ratio of the number of skeletal complications experienced by a patient divided by the time on the trial by the end of the specified time period.

methods of statistical analysis, based on the occurrence of skeletal related events, must be selected to provide a thorough assessment of the benefits of bisphosphonate treatment.[19]

Evaluations with a primary end point of the time to first adverse event were initially believed to be optimal for establishing the biological efficacy of the agents. Multiple event analyses such as that by Anderson and Gill, however, factor in the number and the timing of all skeletal related events that occur during the study period and may therefore provide a clearer picture regarding the benefits of bisphosphonates.[20]

Who benefits most from bisphosphonates?

Ross confirmed that beneficial effects of bisphosphonates are time dependent; significant benefits were seen only after six months of treatment.[14] It is therefore important to look at survival times for patients with bone only disease and those with disease at other sites, such as concurrent liver metastases.

Plunkett et al performed a retrospective analysis of 859 patients who developed bone metastases from breast cancer to identify factors that predict for complications from skeletal disease.[21] Patients with disease confined to the skeleton were most likely to develop a pathological fracture. The time to fracture of a long bone was similar for all groups, but the least number of fractures occurred in patients with bone and liver metastases, since their survival was the shortest ($P < 0.001$). Patients with bone only disease were most likely to require radiotherapy to painful osseous deposits ($P = 0.0001$) and to develop spinal cord compression ($P = 0.01$).

These results show that patients with disease confined to the skeleton at the diagnosis of bone metastases are most likely to develop skeletal related complications from advanced breast cancer. The observed difference was probably attributable to the survival difference between the groups (the median survival from diagnosis of bone metastases for patients with bone only disease was 2.2 years compared with 5.5 months for patients with bone and liver disease). Patients with bone only disease may therefore benefit most from treatment with bisphosphonates, they are most likely to live long enough to experience the time dependent benefits of bisphosphonates.

Limitations of current studies

The trials of bisphosphonates confirmed a notable benefit for the selected patients involved.[2–13] The problem we are now faced with is how to calculate the amount of benefit in routine clinical practice. Many of these trials clearly contained highly selected patients. Many of the randomised trials of intravenous bisphosphonates limited inclusion to those with an expected prognosis of at least six months (table 2), and, as shown by Ross, the beneficial effects are time dependent.[14] Furthermore, it has been estimated that less than one third of patients in clinical practice will have metastatic disease confined to the skeleton,[21] but about two thirds of patients in the randomised trials of intravenous bisphosphonates had skeletal only disease (table 2). Treatment was therefore inadvertently restricted to a population of patients at greater risk than people with visceral (liver) metastases of developing a skeletal related event as a consequence of their prolonged survival and therefore more likely to obtain the maximum benefit from bisphosphonates. Because bone only disease is less aggressive than visceral metastases, patients live longer—that is, they live long enough to develop skeletal complications; patients with liver metastases usually die within six months. The benefits of bisphosphonates are time dependent—maximum benefit is gained after six months of treatment. A recent survey of Canadian medical oncologists confirmed that most start giving bisphosphonates at the time of diagnosis of bony metastases, and, while acknowledging lack of evidence, they maintain patients on bisphosphonate treatment who have an expected survival of less than six months or even after subsequent skeletal related events and bone progression while taking a bisphosphonate.[22] The rate of skeletal events in clinical practice may therefore be lower than in the highly specified study populations. Therefore the absolute risk reduction becomes smaller, so the reductions seen in the randomised study populations may not be generalisable to the general population. In addition, skeletal related events are defined in many studies as

pathological fracture, spinal cord compression, radiation therapy or surgery to bone, and hypercalcaemia. Although important, this definition does not include many variables that are relevant to patients, such as pain, immobility, use of analgesics, and non-hospital costs, such as physiotherapy. In many of the randomised studies serial radiographs were taken at predefined intervals, searching for asymptomatic skeletal related events,[3 16] thereby ignoring pain, which is the most commonly expressed symptom in patients with bone metastases.[23]

Future directions

Further investigation is needed to clarify the benefits of bisphosphonate treatment in patients with extensive metastases and a poorer overall prognosis than those enrolled on the randomised trials. Until such data become available, it may be an appropriate and cost effective strategy in patients with asymptomatic bone disease to delay the initiation of bisphosphonates or avoid it altogether in patients with a prognosis of less than six months.

The optimal time for both starting and stopping treatment is unknown. Guidelines from the American Society Of Clinical Oncology suggest initiating treatment when radiological evidence of bone destruction has been obtained and, once initiated, bisphosphonates should be continued until evidence of substantial decline in patients' general performance.[24] A recent study confirmed that 90% of patients continue on bisphosphonates until death despite repeated skeletal related events and bone progression.[25] Although this may be in keeping with these guidelines, the benefit of maintaining patients on bisphosphonate treatment until serious clinical deterioration is unknown. After disease progression, it may be more appropriate to discontinue treatment altogether or change treatment to a more potent bisphosphonate. Studies in this important subgroup of patients, perhaps with quality of life as a primary end point, are clearly warranted.

Furthermore, maintaining patients on bisphosphonates indefinitely has major financial implications. In a post hoc economic assessment of two manufacturer sponsored multinational trials, the costs of pamidronate were projected to exceed greatly the cost savings associated with preventing skeletal related events.[26] Pharmacoeconomic evaluations should be combined with clinical trials to predict the true cost of this supportive treatment accurately and ultimately to assess the optimal use of these agents.

Markers of bone turnover may be helpful in identifying patients likely to respond to bisphosphonate treatment and may also be useful in monitoring the effectiveness of bisphosphonate treatment.[27] Recent work by Brown et al has confirmed the usefulness of the bone resorption marker N-telopeptide (NTx) and the serum bone formation marker bone specific alkaline phosphatase. In a study of 121 patients with metastatic bone disease, patients treated with a bisphosphonate who had a baseline NTx concentration higher than 100 nmol/mmol creatinine were about 20 times more likely (odds ratio 19.5, $P < 0.001$) over the subsequent three months to develop a skeletal complication than patients with normal baseline NTx values.[28]

An exploratory cohort study, in which data were analysed from the placebo arms of the double blind, placebo controlled, international, phase III, zolendronic acid trials in patients with bone metastases from prostate cancer, non-small cell lung cancer, and other solid tumours, showed that high concentrations of each marker at the beginning of the study were significantly associated with an increased risk of negative outcomes, with NTx a stronger prognostic indicator than the serum bone formation marker bone specific alkaline phosphatase. Patients with a high NTx measurement at baseline had a higher risk of experiencing a skeletal related event (relative risk 1.59, 95% confidence interval 1.17 to 2.14, $P = 0.003$), a shorter time to first skeletal related event (1.76, 1.28 to 2.44, $P = 0.001$) and disease progression (1.60, 1.22 to 2.11, $P = 0.001$), and a higher risk of death (2.65, 2.06 to 3.42, $P < 0.001$).[29] Analysis of bisphosphonate treated patients is currently under way.

The ongoing BISMARK study (BISphosphonate therapy directed by bone resorption MARKers) is evaluating the use of bone markers in the timing of bisphosphonate treatment (principal investigator, R Coleman, personal communication, 2004).

Conclusion

Bisphosphonates are now an accepted standard of practice in the management of breast cancer patients with bone metastases. However, it remains an evolving area, and many questions remain unanswered. Although bisphosphonates have clearly revolutionised the treatment of patients with bone metastases, we do not know the optimal use of these agents in all types of patients. Future research is needed to identify factors that predict accurately subgroups of patients who are at highest risk for developing detectable bone metastases and complications and those who would benefit most from treatment. Currently, bone resorption markers seem to have most potential to do this. If proved useful, bone markers will become invaluable tools used in the treatment of bone metastases and may change our current clinical practice.

Contributors: MC and GD had the idea for this article. MCG and MC performed the literature search. All authors contributed to writing the article. MC is guarantor.

Funding: None.

Competing interests: MC and GD have received previous research funding from Novartis Pharmaceuticals and Roche Pharmaceuticals; both companies manufacture bisphosphonates.

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(Accepted 29 January 2005)

Lesson of the week

Atypical presentation of coeliac disease

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Adult coeliac disease is usually associated with a presentation of weight loss, diarrhoea, and malabsorption of nutrients. We are now seeing, however, increased numbers of silent, or subclinical, cases, which are often picked up by the finding of an unexplained anaemia.[1] Despite this change, few clinicians would expect obesity to be part of the presentation. Here we describe four cases that show that we should not be dissuaded from a potential diagnosis of coeliac disease on the basis of a patient's body weight. This is especially pertinent in today's society, where 22% of men and 23% of woman in the United Kingdom are now obese (body mass index > 30).[2]

Case histories

Case 1

A 53 year old woman was referred to the gastroenterology department with an 18 month history of diarrhoea and a background of almost lifelong irregular bowel habit. She had always been overweight, and there had been no recent change. She weighed 131 kg (body mass index 47). Routine blood tests gave normal results apart from mild iron deficiency. She had a test for endomysial antibodies as part of her investigations, and the result was positive. Duodenal biopsies confirmed partial villous atrophy. A bone density (dual energy x ray absorptiometry) scan could not be done because of her weight.

She was put on a strict gluten-free diet and within four months had lost 17 kg. She continued to lose 6.5 kg over the next six months. Her diarrhoea resolved completely.

Case 2

A 51 year old woman was referred by her general practitioner with longstanding dyspepsia and reflux worsened by alcohol and bread. She had always been overweight but had recently noticed a large gain. She weighed 116 kg (body mass index 41) at referral. Results of routine blood tests were normal, other than a vitamin-B12 concentration of 139 (normal 163-490) pmol/l. A test for endomysial antibodies was positive. Duodenal histology confirmed partial villous atrophy, and a bone density scan showed no abnormality.

She was treated with a gluten-free diet and a proton pump inhibitor for her grade 3 reflux oesophagitis. Her weight remained unchanged at follow up, but her symptoms resolved completely.

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The presence of obesity does not exclude coeliac disease

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BMJ 2005;330:773–4