Bisphosphonates' use in metastatic bone disease

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Bisphosphonates already have an established role in the management of the skeletal complications of metastatic bone disease. The development of new, highly potent compounds has led to investigation into their use as preventive agents in the adjuvant setting. The aim of the paper is to evaluate the evidence for their use in prevention and treatment.

Bisphosphonates have been used in treating a range of disorders including metabolic bone disease, Paget's disease and osteoporosis. This review focuses on the evidence underlying their established role in metastatic bone disease, and emerging data on their use in the adjuvant setting to prevent the development of bone metastases, and prevent osteoporosis resulting from premature menopause induced by chemotherapy.

METASTATIC BONE DISEASE

Metastatic bone disease is a major cause of morbidity for cancer patients. Bone pain is the complication of bone metastases most likely to result in patient presentation, others include pathological fracture, spinal cord compression, hypercalcaemia, bone marrow failure, and reduced mobility. Measures to reduce morbidity from skeletal involvement are important for optimizing a patient's quality of life. Metastatic bone disease most commonly results from breast, prostate, lung, renal and thyroid carcinomas (Coleman, 1997), and multiple myeloma.

Bone is the most common site of metastasis in patients with breast cancer, and the majority of women with metastatic breast cancer will eventually develop bone metastases. Patients with bone metastases alone have a longer survival than those with visceral metastases, and up to 20% of patients with metastatic bone disease will still be alive 5 years after diagnosis. Bone metastases are more commonly associated with well-differentiated, oestrogen receptor (ER) positive tumours (Ross et al, 2004).

Bone metastases are frequent in prostate cancer, and most commonly occur in the axial skeleton. Bone metastases from prostate cancer are classically osteoblastic. Patients with prostate cancer are also at a higher risk of osteoporosis owing to androgen deprivation therapy (Heidenreich, 2003).

Bone lesions occur in virtually all patients with advanced stage multiple myeloma, and most morbidity in this disease is related to osteolytic bone metastases and their complications.

MECHANISM OF ACTION OF BISPHOSPHONATES

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption. They bind avidly to the bone mineral and accumulate in bone at sites of active bone metabolism where they achieve therapeutic concentrations. Bisphosphonates are released during bone resorption, internalized by osteoclasts, inhibiting their activity and causing apoptosis (Green, 2002).

Several generations of bisphosphonates have been developed with increasing potency being achieved by modification of the R2 side chain (*Figure 1*). Results cannot be extrapolated from one bisphosphonate to another as small changes in the chemical structure can have significant effects on chemical properties.

First-generation bisphosphonates, clodronate and etidronate, do not contain a nitrogen atom.

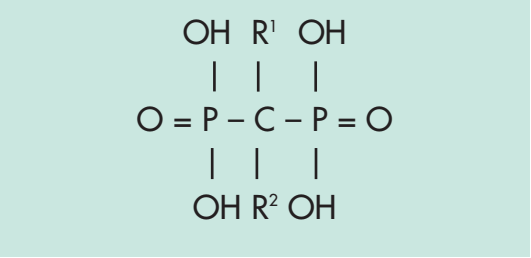

Figure 1. Basic structure of bisphosphonates.

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Once internalized by osteoclasts they act as analogues of adenosine triphosphonate and inhibit adenosine triphosphonate-dependent intracellular enzymes, resulting in a cytotoxic effect and osteoclast apoptosis (Rogers et al, 1999).

Nitrogen-containing bisphosphonates, including pamidronate, alendronate, zoledronate, and ibandronic acid, have an R2 side chain that contains one or two nitrogen atoms. Nitrogen-containing bisphosphonates mediate their effects primarily via inhibition of the mevalonate pathway resulting in a decrease in protein prenylation. The relative potencies of bisphosphonates to inhibit bone resorption in rats are shown in *Table 1*.

The mechanism of action of bisphosphonates is still not completely understood, they also affect osteoblasts, and may influence the immune system and inhibit adhesion of tumour cells.

ADMINISTRATION AND ADVERSE EFFECTS

Bisphosphonates are generally well tolerated when administered orally or intravenously. With intravenous administration renal failure is the most serious possible adverse event, particularly in patients taking concomitant non-steroidal anti-inflammatories (NSAIDs), this is avoided by slow intravenous (IV) infusion. Newer, more potent, bisphosphonates can be infused over much shorter durations as the dose of drug required to achieve the equivalent clinical effect is much lower. Both zoledronate and ibandronic acid may be administered as a 15-minute IV infusion, although the latter is in trials and the licensed infusion time is 1 hour. Oral administration may cause gastrointestinal symptoms, and calcium or other foods should be avoided for an hour after dosing as they reduce absorption.

An acute phase reaction commonly occurs 24hours after the first IV infusion of N-BPs causing transient pyrexia, rigors, and occasionally lymphopenia. This does not usually recur after subsequent doses. If hypocalcaemia occurs it is usually mild and can be corrected with calcium and vitamin D supplements. Other adverse effects are ophthalmic complications (uveitis, scleritis, and episcleritis), and transient exacerbation of bone pain (Adami and Zamberlan, 1996).

TABLE 1.
Relative potency of bisphosphonates to inhibit bone resorption in rats

Clodronate	x10
Etidronate	x10
Pamidronate	x100
Alendronate	x100-1000
Risedronate	x1000-10,000
Ibandronic acid	x1000-10,000
Zoledronic acid	x>10,000

From: Ross et al, 2004.

BISPHOSPHONATES IN ESTABLISHED METASTATIC BONE DISEASE

A recent meta-analysis of 30 studies has confirmed the benefit of bisphosphonates in reducing skeletal morbidity in patients with metastatic bone disease from a variety of primary cancers but mainly breast, prostate and myeloma (Ross et al, 2003). Bisphosphonates compared to placebo, significantly reduced the odds ratios for vertebral and non-vertebral fractures, the need for radiotherapy, and hypercalcaemia (all $P<0.001$). Incidence of spinal cord compression ($P=0.113$) and need for orthopaedic surgery ($P=0.698$) were not significantly reduced. This translates to patients taking bisphosphonates having 65% of the risk of a skeletal-related event compared to patients not taking bisphosphonates.

Ten studies reported time to first skeletal-related event and, although the data could not be combined owing to heterogeneity, eight studies showed a significant increase in the bisphosphonate-treated group (Ross et al, 2003).

Breast cancer

Bisphosphonates have been shown to be beneficial in breast cancer patients with metastatic bone disease who are also receiving either chemotherapy or endocrine therapy. Concomitant administration of pamidronate 90 mg IV over 2 hours on a monthly basis for 12 months was compared with placebo in 382 women with breast cancer and at least one lytic bone lesion who were receiving chemotherapy (Hortobagyi et al, 1996). The median time to occurrence of first skeletal complication was greater in the pamidronate group than the placebo group (13.1 *vs* 7.0 months, $P=0.005$), and the proportion of patients in whom any skeletal complication occurred was lower at 6 months (35% *vs* 47%, $P=0.02$) and this effect was increased at 12 months (43% *vs* 56%, $P=0.008$). The beneficial effects of pamidronate appeared to accumulate over time with some outcome measures such as the proportion of patients with new non-vertebral pathological

fractures being significantly reduced only at 12 months.

Theriault et al (1999) compared the same pamidronate regimen for up to 2 years with placebo in 372 women receiving hormonal therapy. The time to first skeletal complication was longer for patients receiving pamidronate than for those given placebo (P=0.049). At 24 cycles the proportion of patients having had any skeletal complication was 56% in the pamidronate group and 67% in the placebo group (P=0.027).

Ibandronic acid is a third-generation nitrogen-containing bisphosphonate that is 50–100 times more potent than pamidronate in animal studies. The efficacy of intravenous ibandronic acid 6mg every 3–4 weeks in metastatic bone disease owing to breast cancer has been confirmed in a randomized, placebo-controlled trial of 2 years' treatment in 466 patients (Body et al, 2003). The skeletal morbidity period rate was significantly lower in the ibandronic acid 6 mg group (P=0.004 *vs* placebo), as was the reduction in number of new bone events and the increase in time to first new bone event. Ibandronic acid 6 mg was well tolerated. In particular, there was no evidence of renal toxicity.

Ibandronic acid is also available as an oral preparation, 50 mg daily, taken as one tablet in the morning, 1 hour before breakfast with a glass of water. Pooled data from two phase III placebo-controlled studies of 564 patients with breast cancer and bone metastases randomized to ibandronic acid 50 mg daily or placebo for up to 96 weeks showed a significant reduction in the mean skeletal morbidity period rate for the ibandronic acid group compared to placebo (P=0.004) (Body et al, 2004). There was also a significant reduction in the number of events requiring radiotherapy (P<0.001) and surgery (P=0.037). The incidence of mild upper gastrointestinal side effects was slightly higher with oral ibandronic acid but otherwise it was well tolerated.

Alleviation of bone pain is an important aspect of the palliative care of patients with metastatic bone disease. Many patients experience bone pain which is often difficult to control, especially if it becomes resistant to opioids and NSAIDs. Bisphosphonates may reduce bone pain by inhibiting osteoclast-mediated bone resorption and decreasing the release of pain-stimulating cytokines (Body et al, 1998). Three randomized, placebo-controlled, double-blind studies investigating the effects of ibandronic acid in alleviating bone pain in women with metastatic breast cancer have shown that both IV and oral preparations significantly reduce bone pain scores compared to placebo (P=0.001) (Tripathy et al, 2003). The effect was maintained throughout a 2-year period. Oral ibandronic acid also reduced analgesic consumption (P=0.019), and pain reductions with ibandronic acid were associated with improvements in quality of life.

Ibandronic acid is a well tolerated, effective oral bisphosphonate which may be more convenient than IV bisphosphonates for patients, because it allows self-administration at home without the need for regular hospital attendances. A comparative trial is currently planned to examine the effects of oral ibandronic acid and IV zoledronate in patients with metastatic bone disease owing to breast cancer.

Prostate cancer

The largest trial investigating bisphosphonates in hormone-refractory prostate cancer metastatic to bone randomized 643 men to receive either zoledronate 4 mg every 3 weeks for 15 months or placebo (Saad et al, 2002). There was also a zoledronate 8 mg arm which was discontinued due to occurrence of renal insufficiency. A 5-minute infusion was also discontinued for the same reasons. There was a significant reduction in skeletal-related event between the zoledronate 4 mg group and the placebo group (33% *vs* 44%, P=0.02). The time to first skeletal event was also significantly prolonged.

Myeloma

The mainstay treatment of symptomatic myeloma is chemotherapy. However, skeletal disease commonly progresses despite the attainment of stable disease (Kanis and McCloskey, 2000). In a prospective trial of 536 patients, oral clodronate therapy (1600 mg daily) for a median of 34 months compared to placebo caused a significant reduction in nonvertebral fractures (6.8% *vs* 13.2%, P<0.05), and vertebral fractures (37.9% *vs* 55.0%, P=0.02) (McCloskey et al, 1998). Four weekly 90mg pamidronate infusions over 9 months in 392 patients also receiving chemotherapy lead to significant decreases in requirements for radiotherapy to bone (14% *vs* 22%, P<0.05), pathological fracture (17% *vs* 30%, P=0.004), and time to first skeletal event (P=0.001) (Berenson et al, 1996).

No studies to date have demonstrated a significant survival advantage with bisphosphonate treatment in patients with established metastatic bone disease from any primary cancer (Ross et al, 2004). However, quality of life is paramount in this patient group and a reduction in the risk of skeletal-related events or time to first skeletal-related event is likely to have a significant

impact on patients' quality of life.

In the absence of data on optimal duration of therapy the current recommendation, based on expert opinion, is that, once initiated, bisphosphonates should be continued until there is a substantial decline in a patients' performance status (Hillner et al, 2000).

There is no evidence that treatment with bisphosphonates for less than 6 months has an impact on skeletal morbidity, and it may therefore be inappropriate to treat patients who have a poor prognosis.

HYPERCALCAEMIA

Intravenous bisphosphonates are now the drug of choice for the treatment of acute hypercalcaemia of malignancy, together with IV fluids to correct dehydration. Zoledronate has the advantage of a shorter (usually 15-minute) infusion time compared to pamidronate which needs to be given over 2 hours. A pooled analysis of two randomized controlled trials comparing a single dose of zoledronate (4 mg or 8 mg) via 5-minute infusion with pamidronate (90 mg) via 2-hour infusion in patients with moderate-to-severe hypercalcaemia of malignancy (corrected serum calcium ≥3.00 mmol/litre) showed significant advantages with zoledronate (Major et al, 2001). Mean corrected serum calcium levels at days 4, 7, and 10 were significantly ($p<0.05$) lower in patients treated with either 4mg or 8mg zoledronate than in patients treated with pamidronate, as was the proportion of patients with normalisation of serum calcium levels (to ≤2.70 mmol/litre) by day 7. Median time to relapse was also longer in patients treated with zoledronate 4 mg (30 days, $P=0.001$) or zoledronate 8 mg (40 days, $P=0.007$) compared to pamidronate (17 days).

Ibandronic acid is also licensed for hypercalcaemia of malignancy and has shown superiority over pamidronate (Pecherstorfer et al, 2003)

ADJUVANT BISPHOSPHONATE THERAPY

Current therapeutic options in metastatic bone disease are mainly palliative; therefore, effective prevention strategies would represent an important clinical advance. The effectiveness of bisphosphonates in managing established metastatic bone disease and evidence from *in-vitro* and animal studies has led to studies investigating a possible role for bisphosphonates as adjuvant treatment for prevention of bone metastases.

Pre-clinical studies

In-vitro studies have shown that bisphosphonates inhibit proliferation and induce apoptosis of a variety of human tumour cell lines at relatively low concentrations (in the range 10–100 µmol/litre), including breast cancer, prostate cancer, myeloma, and melanoma cell lines (Clézardin, 2002). Bisphosphonates may inhibit metastasis to bone by affecting adhesion of tumour cells to the bone extracellular matrix and by inhibiting the process of invasion through the extracellular matrix (Boissier et al, 1997). Studies have also suggested that bisphosphonates have antiangiogenic effects. However, the underlying mechanisms responsible for these effects are not clearly understood. Interestingly, the combination of zoledronate with standard anticancer drugs, including paclitaxel, tamoxifen, and dexamethasone results in synergistic apoptotic effects on breast cancer cell lines (Jagdev et al, 2001).

Animal Models

The *in-vitro* findings are supported by data from tumour xenograft models in animals showing that nitrogen-containing bisphosphonates can reduce tumour-induced osteolysis, inhibit the progression of existing bone lesions, prevent development of new bone metastases, and reduce skeletal tumour burden (Coleman, 2002). However, the majority of animal studies used frequent subcutaneous injection, and it is not known whether the same antitumour potential would be achieved using an intermittent IV administration that is currently used clinically.

Clinical evidence

Oral clodronate has been investigated as a potential adjuvant therapy to prevent the development of bone metastases in patients with primary breast cancer. Diel et al (1998) randomized 302 patients with primary breast cancer (node positive and node negative) and tumour cells in bone marrow aspirates, a risk factor for the development of bone metastases, to either 2 years of oral clodronate 1600 mg daily or standard follow-up. All patients received standard surgical treatment and hormonal or chemotherapy. After a median follow-up of 36 months, bone metastases were detected in 12 patients (8%) in the clodronate group and 25 patients (17%) in the control group ($P=0.003$). The incidence of visceral metastases was also decreased ($P=0.003$). Six patients died in the clodronate group as did 22 in the control group. Therefore, clodronate also conferred a significant overall survival benefit ($P=0.001$). An update of the data at 55 months' follow-up showed a continuing significant survival benefit ($P=0.002$) and reduction in bone metastases

(P=0.044), but no significant reduction in visceral metastases. A further update at 103 months' follow-up again shows a survival benefit although with reduced significance (P=0.049), and no significant reduction in either bone or visceral metastases (Diel et al, 2004). The authors concluded that 2 years of clodronate reduces mortality, but perhaps a longer duration of therapy might prevent later metastases.

A second placebo-controlled trial of 2 years' treatment with oral clodronate in 1069 primary breast cancer patients with a median follow-up of 5.5 years showed a similar reduction in occurrence of bone metastases (P=0.016) and increased overall survival (P=0.047) in the clodronate-treated group (Powles et al, 2002). However, the reduction in occurrence of bone metastases only remained significant while patients remained on treatment, and significance was lost when the analysis was performed for the total follow-up period (P=0.127). There was no significant reduction in visceral metastases. This data imply that the beneficial effects of bisphosphonates may not be maintained once patients stop treatment, an important consideration for adjuvant therapy.

A third trial of adjuvant clodronate for 3 years in 299 women with node-positive primary breast cancer with a median follow up of 5 years showed no difference in the incidence of bone metastases, and conversely showed a significant increase in visceral metastases, and a shorter overall survival for clodronate treated patients (Saarto et al, 2001). However, this trial recruited only 282 patients, was not placebo-controlled, and had a significant imbalance for hormone receptor status in the two arms.

Adjuvant clodronate in primary breast cancer is being evaluated further by ongoing clinical trials such as the National Surgical Adjuvant Breast and Bowel Project B-34 trial. The UK-based AZURE study will examine 5 years of adjuvant zoledronate therapy in patients with stage II/III breast cancer who also receive chemotherapy and/or hormonal therapy.

OSTEOPOROSIS FOLLOWING ADJUVANT THERAPY FOR PRIMARY BREAST CANCER

Adjuvant chemotherapy commonly induces premature ovarian failure in premenopausal women, and this patient group has a 14% lower mean lumbar bone mineral density compared with those who continue to menstruate (Bruning et al, 1990). In postmenopausal women, tamoxifen can increase bone mineral density although fracture rates are unaltered. In premenopausal women tamoxifen decreases bone mineral density (Powles et al, 1996).

Bisphosphonates have shown activity in preventing osteoporosis in this patient group. Delmas et al (1997) showed that 2 years' treatment with risedronate in 53 women with chemotherapy-induced menopause led to preservation of baseline bone mineral density at the lumbar spine, while patients not on treatment experienced reductions in bone mineral density. On cessation of treatment bone loss ensued, suggesting continued treatment is necessary. In a study of 300 patients receiving chemotherapy and/or tamoxifen for primary breast cancer, 2 years' treatment with clodronate significantly reduced loss of bone mineral density in the lumbar spine, hip, and trochanter compared to placebo (Powles et al, 1998).

Recent studies have indicated that yearly IV infusions of zoledronate can increase bone mineral density, and further trials are ongoing with this treatment strategy. Confirmation that preservation of bone mineral density leads to reduced fracture rates is also required.

CONCLUSIONS

Bisphosphonates have an established role in the management of metastatic bone disease and hypercalcaemia of malignancy, and their use as adjuvant agents to prevent development of bone metastases and treatment-induced osteoporosis is the subject of ongoing studies. Oral bisphosphonates allow the convenience of self-administration at home in a patient group where quality of life is paramount, and trials comparing the effects to IV administration are currently planned. **HM**

Conflict of interest: This article has been supported by Roche Products

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KEY POINTS

- Skeletal complications of metastatic bone disease are common among cancer patients and can severely affect quality of life.
- Bisphosphonates significantly reduce skeletal complications in established metastatic bone disease but the optimum point to initiate treatment is unknown.
- Adjuvant bisphosphonate therapy in breast cancer patients may reduce the incidence of bone metastases and improve overall survival. Further trial data is awaited.
- Chemotherapy-induced osteoporosis is a significant problem, particularly in premenopausal women with breast cancer, and bisphosphonates may help prevent loss of bone mineral density.
- Oral bisphosphonates such as ibandronic acid are attractive owing to patient convenience, and trials comparing the effects with intravenous agents are planned.