Managing cancer-related skeletal events with bisphosphonates

Simon Rule

Bone metastases cause considerable morbidity. This article discusses the benefits of bisphosphonates, which are now well established in the treatment of skeletal complications across a wide range of tumour types.

The bone is the organ most commonly affected by metastatic cancer (Coleman, 1997), particularly with carcinomas of the breast, lung, prostate, kidney and thyroid, and multiple myeloma (*Table 1*; Rubens and Coleman, 1995; Coukell and Markham, 1998). The highest prevalence of bone metastases is associated with carcinomas of the breast and prostate, accounting for over 80% of cases (Coleman, 2000a).

Bone metastases most frequently affect the highly vascularized parts of the skeleton, in particular the red bone marrow of the axial skeleton, the proximal ends of the long bones, the ribs and the vertebral column. The main determinant of the site of metastasis is blood flow from the primary site (Mundy, 1999). Patients with bone metastases have prolonged survival compared to patients with other sites of metastases, which can result in significant morbidity over a prolonged period of time (Berenson, 1997).

CLINICAL CONSEQUENCES OF BONE METASTASES

Bone metastases cause considerable morbidity, with bone pain being the commonest and most debilitating symptom (Mundy, 1999; Coleman, 2000a). Pathological fractures following trivial injury occur most commonly in patients with osteolytic lesions, with ribs and vertebrae commonly affected. Vertebral destruction by osteolytic lesions, leading to fragility of the vertebral body and consequent spinal deformity, can result in nerve compression. This can cause excruciating pain and may require stabilization of the spine – a major operation which itself can cause significant mortality and morbidity (Mundy, 1999; Coleman, 2000a).

Tumour-induced hypercalcaemia (TIH) is the most common metabolic disorder associated with cancer (Berenson, 1997; Coleman, 1997). It is essentially the result of a marked stimulation of osteoclast-mediated bone resorption (Body, 2000). Untreated, it is usually progressive and causes the patient's condition to deteriorate rapidly (Barnett, 1999).

TABLE 1.
Incidence of bone metastases

Type of cancer	Incidence
Myeloma	95–100%
Breast	65–75%
Prostate	65–75%
Lung	30–40%
Kidney	20–25%
Thyroid	60%
Melanoma	14–45%

CLASSIFICATION OF BONE METASTASES

Bone metastases usually fall into three categories: lytic, sclerotic or mixed, with the classification depending upon the radiographical appearance of the lesions (Coleman, 2000a). For example, where bone resorption predominates, focal bone destruction occurs and the metastases are lytic in appearance (Coleman, 1997). These lytic lesions are commonly found in multiple myeloma, breast, lung, thyroid, renal, melanoma and gastrointestinal malignancies (Coleman, 2000a). Conversely, in bone metastases characterized by increased osteoblastic activity, the lesions appear sclerotic (Coleman, 1997). Metastases from prostate carcinoma in particular give rise to sclerotic lesions (Clarke, 1998).

BONE STRUCTURE

Bone consists of two different structures. The outer cortical layer is a hard mineralized matrix,

Dr Simon Rule is Consultant Haematologist in the Department of Haematology, Derriford Hospital, Plymouth PL6 8DH

making up 85% of the total bone in the body. This matrix is most abundant in the long bones. Cancellous or trabecular bone constitutes the remaining 15% of the skeleton and predominates in the vertebral bodies (Guise and Mundy, 1998).

BONE REMODELLING

Bone remodelling is a coordinated process of resorption and new bone formation, essential for bone strength, which occurs in response to mechanical stress. Osteoclasts are responsible for bone resorption, while bone formation is mediated by osteoblasts (Rubens and Coleman, 1995). Osteoclast-mediated resorption usually takes about 7–10 days, while the subsequent formation phase spans about 3 months.

Local factors produced in the bone marrow regulate the remodelled bone (Guise and Mundy, 1998). Coupling factors, which stimulate bone formation, govern cellular events such as recruitment of osteoblastic precursors to the defective site, development of mature osteoblasts and bone formation (Guise and Mundy, 1998).

In the pathological state (*Figure 1*), malignant cells secrete factors that stimulate, both directly and indirectly, osteoclast activity (Rubens and Coleman, 1995). These include parathyroid hormone-related protein (PTHrP), interleukin-1 (IL-1), prostaglandin E (PGE_2), transforming growth factors (TGF) α and β, epidermal growth factor and tumour necrosis factor.

Tumour cells may also promote bone resorption by stimulating tumour-associated immune cells to release osteoclast-activating factors (Rubens and Coleman, 1995). Tumour-induced osteoclastic bone resorption also enriches the bone microenvironment further with bone-derived growth factors that enhance the survival of the tumour cells (Guise and Mundy, 1998).

In addition to the changes in the bone microenvironment described above, production of systemic factors such as PTHrP by the primary tumour can stimulate osteoclast-mediated bone resorption, resulting in hypercalcaemia in the absence of bone metastases (Rubens and Coleman, 1995).

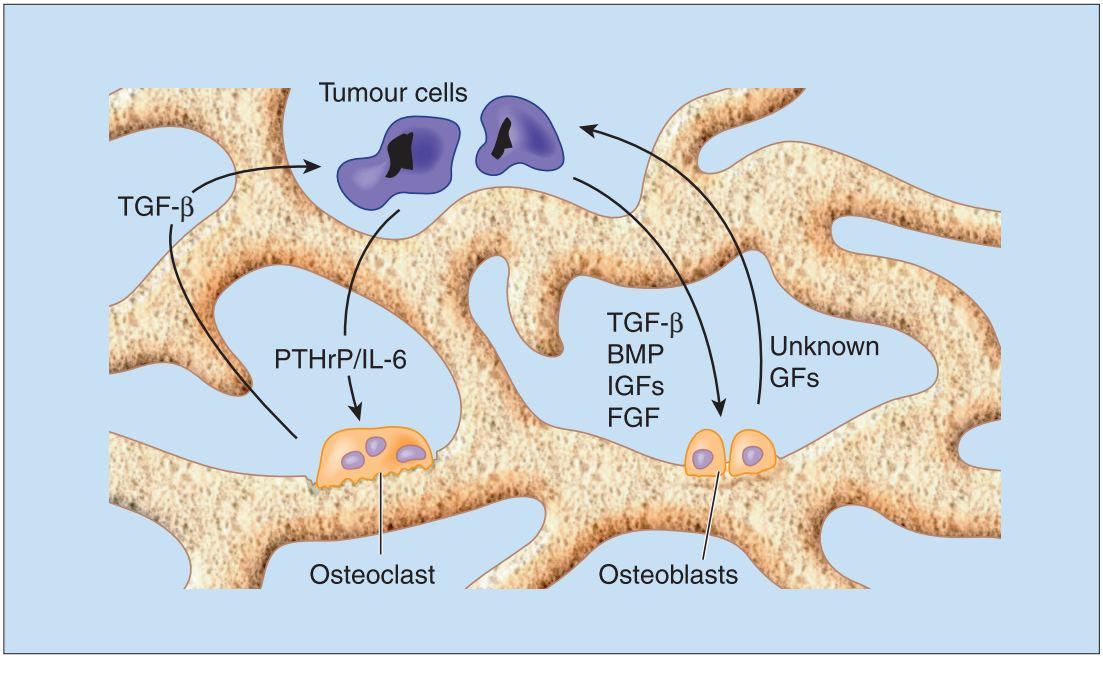
With some tumours, new bone formation is not necessarily preceded by bone resorption. Prostate tumour cells have been shown to produce osteoblastic growth factors such as TGF-β and platelet-derived growth factor (Rubens and Coleman, 1995).

TREATMENT OF BONE METASTASES

With only very rare exceptions, the treatment of bone metastases is palliative and there are no reliable data to indicate that early diagnosis of bone metastases improves survival (Coleman, 1998). Nevertheless, a delay in diagnosis undoubtedly leads to physical and psychological distress.

Systemic treatment of bone metastases consists of two main approaches: direct antitu-

Figure 1. Pathogenesis of osteolytic bone metastasis. BMP = bone morphogenetic protein; FGF = fibroblast growth factor; GF = growth factor; IGF = insulin-like growth factor; IL-6 = interleukin 6; PTHrP = parathyroid hormone-related protein; TGF-β = transforming growth factor β.



mour action to inhibit the production of growth factors (by surgery, radiotherapy, chemotherapy, endocrine treatments and/or the use of bone-seeking isotopes), and blocking the effects of such growth factors on host cells (with bisphosphonates, anti-inflammatory agents or calcitonin; Coleman, 2000a). External beam radiotherapy provides excellent palliation for localized bone metastases, however, for patients with widespread poorly localized bone pain or recurrence of bone pain in previously irradiated sites, bisphosphonates offer another form of treatment (Coleman, 2000a).

Bisphosphonates are potent inhibitors of normal and pathological bone resorption (Rodan, 1998). Until recently, their complex molecular mechanism was poorly understood (Rodan, 1998), but trials now suggest that aminobisphosphonates (such as alendronate) and non-aminobisphosphonates (such as clodronate) have two distinct molecular mechanisms. Alendronate causes apoptosis by preventing post-translational modification of GTP-binding proteins with isoprenoid lipids, whereas clodronate is metabolized intracellularly to form a cytotoxic β-γ-methylene (AppCp type) analogue of ATP (Benford et al, 1999).

All bisphosphonates are characterized by a P–C–P bond in their structure (*Figure 2*), which promotes their binding to the mineralized bone matrix and subsequent inhibitory effects on bone resorption (Coleman, 1998). In the early 1990s, extensive clinical research was undertaken using the newly discovered bisphosphonates. They have become the standard treatment for TIH (Blamey, 1999) and a valuable new form of therapy for cancer-related skeletal events arising from both lytic and sclerotic lesions.

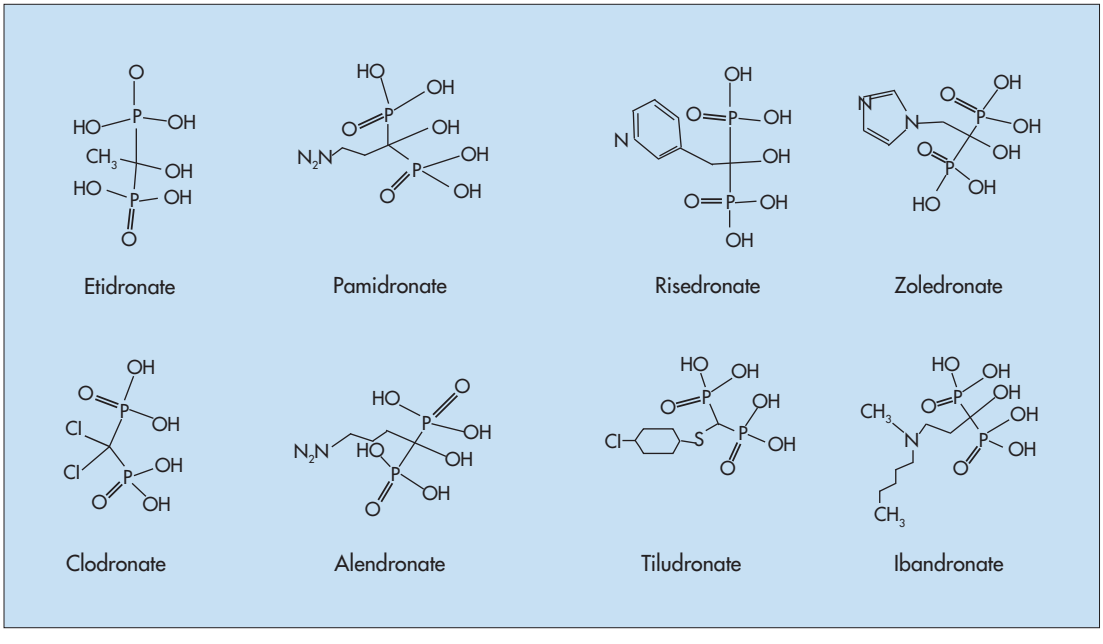
BREAST CARCINOMA AND MULTIPLE MYELOMA

The inhibitory effects of bisphosphonates on bone resorption have directed the majority of research to their clinical benefits in tumours producing lytic lesions – carcinoma of the breast and multiple myeloma.

Of the first-generation bisphosphonates introduced in the 1980s, etidronate inhibits bone mineralization as well as resorption (Body et al, 1998; Lipton, 1998), however, oral etidronate was shown to be ineffective when added to chemotherapy in patients with newly diagnosed myeloma patients (Berenson et al, 1996). Oral clodronate showed more promising results: 1600 mg daily reduced the number of new vertebral fractures after the first year of treatment in myeloma patients, when given at the time of diagnosis (McCloskey et al, 1995). Although no significant differences in non-vertebral fractures or radiation therapy were observed in a randomized, double-blind placebo-controlled study in patients with metastatic breast cancer, the combined rate of all skeletal-related events (SREs) was significantly reduced (Paterson et al, 1993).

The benefits of the second-generation aminobisphosphonate pamidronate are well established. Pamidronate is more potent than

Figure 2. Structure of bisphosphonates.



clodronate and inhibits bone resorption at doses which do not inhibit mineralization (Lipton, 1998).

The efficacy of pamidronate infusions has been unequivocally demonstrated in patients with myeloma and metastatic breast cancer (Berenson et al, 1996; Lipton, 1998). In a 2-year double-blind, placebo-controlled study of patients with stage 3 multiple myeloma and at least one lytic lesion, pamidronate 90 mg, infused over 4 hours every 4 weeks, significantly reduced the proportion of patients who had any skeletal events compared with placebo (Berenson et al, 1996). Patients who received pamidronate also had less bone pain and a delayed deterioration in performance status and quality of life.

A pooled analysis of two prospective, placebo-controlled, randomized clinical trials of breast cancer patients with at least one untreated lytic lesion 1 cm in diameter (one trial in patients with stage 4 breast cancer who were receiving cytotoxic chemotherapy, the other in patients receiving endocrine therapy) revealed that the proportions of patients having had any SREs (except TIH), radiation administered to bone and any pathological fractures, were significantly less in the pamidronate group than in the placebo group (Lipton, 1998). Further benefits seen in the pamidronate group included less increase in bone pain, less increase in the use of narcotics and slower deterioration in performance status.

Breast cancer data are also available with oral ibandronate. A randomized, placebo controlled, phase III trial involving 846 patients with breast cancer and confirmed bone metastases found that, compared to placebo, ibandronate (50 mg/day for 96 weeks) evoked significant improvements in time-adjusted skeletal morbidity period rate (P=0.004), and significant reductions in events requiring radiotherapy and surgery. The mean number of bone events per patient was also significantly reduced (P=0.008) (Tripathy et al, 2003).

Zoledronate (zoledronic acid) is a third-generation bisphosphonate, which has approximately 87- to 940-fold greater potency than pamidronate in pre-clinical models of bone resorption (*Table 2*; Green et al, 1994). Its side chain consists of an imidazole ring side chain containing two critically placed nitrogen atoms. Nitrogen-containing bisphosphonates are known to inhibit the mevalonate pathway, which governs post-translational modification of GTP-binding proteins, resulting in osteoclast apoptosis (Coleman, 2000b).

Clinical studies have demonstrated the efficacy of zoledronate in treating skeletal complications of malignancy. A pooled analysis of two randomized double-blind trials in patients with moderate to severe TIH demonstrated that zoledronate 4 mg or 8 mg infused over 5 minutes was superior to pamidronate 90 mg infused over 2 hours (Major et al, 2001). Treatment with zoledronate was associated with a higher proportion of patients showing a complete response, a more rapid normalization of serum calcium, and a longer time to relapse compared to pamidronate. The 4 mg dose of zoledronate was as effective as the 8 mg dose in the TIH population as a whole. Adverse events occurred with similar frequency in the zoledronate 4 mg and 8 mg groups and the pamidronate 90 mg group.

The efficacy of zoledronate in the treatment of skeletal complications of malignancies has also been evaluated in a range of tumour types, including breast, multiple myeloma, prostate, non-small cell lung cancer, and other solid tumours (Rosen et al, 2001a; Lipton et al, 2002). In a double-blind comparative trial in patients with stage 3 multiple myeloma with at least one osteoporotic lesion or breast cancer patients with at least one bone metastasis, a 15-minute infusion of zoledronate 4 mg every 3–4 weeks had a similar effect to a 2-hour infusion of pamidronate 90 mg. Zoledronate 4 mg was associated with significantly lower radiation therapy to bone and sub-group analysis revealed a significant delay in time to first SRE in breast cancer patients with lytic metastases. Again, zoledronate 4 mg and pamidronate 90 mg were equally well tolerated; the most common adverse events were bone pain, nausea, fatigue and fever.

PROSTATE AND OTHER SOLID TUMOURS

Bone metastases in prostate carcinoma are predominantly sclerotic in nature and can cause

TABLE 2.
Relative potencies of current bisphosphonates

Bisphosphonate	Relative potency
Etidronate	1
Clodronate	10
Pamidronate	100
Risedronate	1000
Alendronate	10 000
Ibandronate	50 000
Zoledronate	100 000

From Hillner et al (2000)

considerable morbidity and pain. The utility of bisphosphonates in preventing skeletal complications in prostate cancer has been investigated with mixed results.

A randomized placebo-controlled study of etidronate in 57 patients with metastatic prostate cancer was unable to demonstrate any improvement in pain scores (Smith, 1989).

Pamidronate has been shown to preserve bone mineral density in patients with prostate cancer post orchidectomy and during androgen deprivation therapy (Clarke et al, 1992; Smith et al, 2001). In hormone-escaped metastatic prostate cancer, 6 months' treatment with pamidronate improved pain scores and Karnofsky performance status, although this effect was not universal (Clarke et al, 1992).

Clodronate has also shown some efficacy in reducing pain scores in patients with symptomatic bone metastases and hormone-escaped metastatic prostate cancer (Vorreuther, 1993; Cresswell et al, 1995). Two large double-blind placebo-controlled multicentre studies are currently being conducted by the Medical Research Council to evaluate whether long-term treatment with oral clodronate protects skeletal integrity and minimizes development of painful skeletal symptoms and whether clodronate protects the skeleton from metastatic spread. The first of these studies (PR05) showed no significant benefits for clodronate in any of the endpoints evaluated.

The efficacy of zoledronate in treatment of skeletal complications of malignancy associated with prostate and other solid tumours deserves special mention, as the studies described below are the first to report benefits for patients treated with a bisphosphonate in these tumour types.

In a double-blind randomized placebo-controlled trial in patients with hormone-refractory prostate cancer with at least one bone metastasis, zoledronate 4 mg infused over 15 minutes every 3–4 weeks for 15 months significantly reduced the proportion of patients with an SRE and the proportion with a pathological fracture (Saad et al, 2002). Zoledronate also significantly delayed the time to first SRE and pathological fracture, and attenuated the increase in pain scores seen over the duration of the study (Saad et al, 2002).

Similar results were seen in patients with tumours other than breast, myeloma and prostate cancer (51% were lung, primarily non-small cell) treated with zoledronate 4 mg every 3 weeks for 9 months (Rosen et al, 2001b). Zoledronate significantly decreased the proportion of patients with one SRE and prolonged the time to first SRE (Rosen et al, 2001b).

POSSIBLE DIRECT ANTITUMOUR EFFECT OF BISPHOSPHONATES

There is indirect evidence from in-vitro studies to suggest that zoledronate may have direct antitumour effects. Pretreatment of breast and prostate carcinoma cells with bisphosphonates directly inhibits tumour cell invasion and adhesion to bone (Boissier et al, 1997, 2000). Zoledronate was the most potent of the bisphosphonates tested, and the evidence suggested that the possible antitumour effect of bisphosphonates is strongly associated with the structure of the side chain (Boissier et al, 2000). In multiple myeloma cells, pamidronate and zoledronate both demonstrated a dose- and time-dependent cytotoxic effect, with zoledronate-induced cytotoxicity significantly greater than that for pamidronate (Aparicio et al, 1998).

TREATMENT-INDUCED BONE LOSS

Evidence also suggests that bisphosphonates can play a major role in alleviating or preventing treatment-induced bone loss. A randomized, 5-year study of 73 premenopausal women with chemotherapy-induced (cyclophosphamide, methotrexate, 5-fluorouracil; CMF) ovarian failure investigated the bone-preserving properties of oral clodronate treatment (1600 mg/day for 3 years). At the end of the study period, patients were divided into those with preserved menstruation and those with amenorrhoea. Changes in bone mineral density correlated significantly with post-chemotherapy menstrual function.

Three-year clodronate treatment significantly reduced the bone loss in the lumbar spine (–3.0% compared to controls –7.4%; P=0.003) at 3 years, and these differences were still present after 5 years (–5.8% *vs* –9.7%; P=0.008). The authors concluded that although chemotherapy-induced ovarian failure caused a temporary accelerated bone loss of the lumbar spine, it was significantly reduced by adjuvant clodronate therapy, even 2 years after the termination of treatment (Vehmanen et al, 2001).

CONCLUSIONS

The benefits of bisphosphonates in the treatment of the skeletal complications of malignancy across a wide range of tumour types has now been established, providing a further addition to the armamentarium of clinicians who treat these patients. HM

Conflict of interest: Dr Rule has attended scientific conferences and presented at lectures for various pharmaceutical companies including AstraZeneca, Novartis Oncology, Pfizer and Roche.

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KEY POINTS

- Bone metastases are a common complication of cancer.
- Bone metastasis is a catastrophic complication for most patients, resulting in significant morbidity and loss of quality of life.
- Treatment options for metastatic bone disease include direct antitumour treatments such as surgery, radiotherapy, chemotherapy, endocrine therapy or bone-seeking isotopes.
- Bisphosphonates have become the agents of choice for the treatment of skeletal complications of malignancy, showing good clinical efficacy across a range of tumour types.
- Recent studies suggest that the more potent bisphosphonates, e.g. zoledronate, have therapeutic advantages.
- In-vitro studies suggest more potent bisphosphonates may also exert a direct antitumour effect, but this requires further evaluation in the clinical setting.