Management of Bone Metastases

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ABSTRACT

Metastatic bone disease develops as a result of the many interactions between tumor cells and bone cells. This leads to disruption of normal bone metabolism, with the increased osteoclast activity seen in most, if not all, tumor types providing a rational target for treatment. The clinical course of metastatic bone disease in multiple myeloma, breast and prostate cancers is relatively long, with patients experiencing sequential skeletal complications over a period of several years. These include bone pain, fractures, hypercalcemia, and spinal cord compression, all of which may profoundly impair a patient’s quality of life.

External beam radiotherapy and systemic endocrine and cytotoxic treatments are the mainstay of treatment in advanced cancers. However, it is now clear that the bisphosphonates provide an additional treatment strategy, which reduces both the symptoms and complications of bone involvement. Additionally, new specific molecules such as osteoprotogerin have been developed that are based on our improved understanding of the cellular signaling mechanisms involved in cancer-induced bone disease. These potent molecules are now entering clinical trials.

Ongoing research is aimed at trying to define the optimum route, dose, schedule and type of bisphosphate in metastatic bone disease and its use in the prevention and treatment of osteoporosis in cancer patients. In vitro suggestions of direct anticancer activity and some promising clinical data in early breast cancer have resulted in considerable interest in the possible adjuvant use of bisphosphonates to inhibit the development of bone metastases. The Oncologist 2000;5:463-470

INTRODUCTION

The skeleton is the most common organ to be affected by metastatic breast cancer, and the site of disease which produces the greatest morbidity. Skeletal morbidity includes pain requiring radiotherapy, hypercalcemia, pathological fracture, and spinal cord or nerve root compression. From randomized trials in advanced breast cancer [1, 2], it can be seen that one of these major skeletal events occurs on average every three to four months. Additionally, metastatic disease may remain confined to the skeleton with the decline in quality of life and eventual death due entirely to skeletal complications.

There is now a much greater understanding of the mechanisms underlying the development of bone metastases and the interdependence between cancer cells and bone. Tumor cells within the bone marrow cavity secrete a variety of paracrine factors that stimulate bone cell function (Fig. 1).

This stimulation of osteoclast function is of particular importance, resulting in osteolysis which is typically associated with disruption of the normal coupling signals between osteoblast and osteoclast function, and is the rationale for the use of bisphosphonates in the management of metastatic bone disease. These effects on bone cell function may in turn influence serum and urinary levels of biochemical markers of bone metabolism, which may be used to monitor the progress of the disease and response to treatment.

TREATMENT OF BONE METASTASES

Radiotherapy and Radiopharmaceuticals

For the majority of patients, external beam radiotherapy provides excellent palliation for localized metastatic bone pain. In most clinical situations this can be achieved with a short treatment schedule of one to five fractions. Indeed
Resorption is thought to be of minor importance. Release of bone-derived cytokines and growth factors may stimulate tumor cell proliferation.

Figure 1. Interaction of tumor and bone cells within the bone microenvironment. Osteoclastic bone resorption is the principle mechanism. Direct bone resorption is thought to be of minor importance. Release of bone-derived cytokines and growth factors may stimulate tumor cell proliferation.

Role of the osteoclast in bone pathology

Several randomized trials have indicated that a single fraction of 8 Gy is adequate for pain relief [3]. However, further studies are still needed to determine whether these convenient, single or very short schedules are also adequate for patients with a relatively good prognosis. Additionally, very little is known about the effects of different fractionation schedules on the structural quality of the bone—an important consideration in a weight-bearing site.

Radiopharmaceuticals are now available for the palliation of metastatic bone pain. Strontium89 has been shown to be as effective as wide-field radiotherapy in prostate cancer [4] and, because of the preferential uptake of strontium at sites of new bone formation, is probably most effective for sclerotic metastases. However, it may also be of benefit for bone metastases from breast cancer [5]. Samarium153, which is linked to the bisphosphonate ethylene diamine tetramethylene phosphonic acid, has recently been evaluated in prostate and breast cancers. Samarium153 is also preferentially taken up at sites of bone formation, and emits both \( \alpha \) and \( \gamma \) particles. The former allows imaging of the skeleton and the latter provides the therapeutic effects. Samarium153 is suitable for outpatient use, and recent data indicate that the agent has a significant effect on bone pain and analgesic consumption [6]. Further investigation is indicated to compare radioisotope treatment with high-dose bisphosphonates and to determine whether the two treatment approaches complement one another.

Systemic Anticancer Treatment

In selecting systemic antitumour treatment for metastatic bone disease, the pathological type of the tumor is most important. At one extreme, for example, there is little established role for systemic antitumour therapy in renal cell carcinoma and metastatic melanoma, while in lymphoma and germ cell tumors involving bone, combination chemotherapy may be curative.

There have been numerous recent developments in endocrine and cytotoxic treatments that are of relevance to the patient with metastatic bone disease. In breast cancer, the new highly specific aromatase inhibitors letrozole, anastrozole and exemestane are both superior in efficacy and better tolerated than the older agents, megestrol acetate and aminoglutethimide. In multiple myeloma survival has been improved by the selected use of high-dose chemotherapy with bone marrow or peripheral blood stem cell support, while in prostate cancer some trials have suggested that combined endocrine therapy causing total androgen blockade (luteinizing-hormone-releasing-hormone [LHRH] + antiandrogen) may be superior to LHRH analogs alone.

**ORTHOPEDIC SURGERY**

Metastatic destruction of bone reduces its load-bearing capabilities, resulting initially in trabecular disruption and microfractures, and subsequently total loss of bony integrity. Rib fractures and vertebral collapses are most common. These result in loss of height and, when severe and multiple, lead to kyphoscoliosis and a degree of restrictive lung disease. However, it is fracture of a long bone or epidural extension of tumor into the spine that causes the most disability.

The probability of developing a pathological fracture increases with the duration of metastatic involvement. They are therefore, albeit somewhat paradoxically, more common in those patients with bone-only disease who have a relatively good prognosis. Because the development of a fracture is so devastating to a cancer patient, it is important that these patients are assessed by a specialist orthopedic and/or spinal surgeon to advise on the merits of prophylactic surgery. A pathological long-bone fracture in a patient with known metastatic bone disease is really a reflection of inadequate clinical management. With more proactive orthopedic management, it should be possible to intervene before fracture occurs, enabling a simpler and safer operation and with obvious benefits in quality of life for patients.

Fractures are common through lytic metastases and weightbearing bones, the proximal femora being the most commonly affected sites. Damage to both trabecular and cortical bone is structurally important but cortical destruction is most clearly appreciated. Although controversial, several radiological features have been identified which may predict imminent fracture. These include pain, the anatomical site of a lesion, its radiological characteristics, and its size. Although the intensity of bone pain is not directly associated with fracture risk, pain that is exacerbated by movement does appear to be an important factor,
which predicts impending fracture. Radiographic assessment gives information on the size of a lesion and the extent to which the bone is destroyed. When less than one-third of the diameter of a long bone is affected, pathological fracture is relatively unusual, but above this amount and especially when more than 50% of the cortex is destroyed, the fracture rate increases markedly to approximately 80%. A practical scoring system incorporating the above factors has been described to give valuable guidance in the selection of patients for prophylactic fixation [7].

Before surgery, a radionuclide bone scan and radiographs of the entire length of the affected bone should be obtained. This ensures that other lesions within the bone are recognized, stabilized when necessary and included in the radiotherapy field. A pathological fracture at the edge of a plate or an intramedullary nail, particularly when fixed with methyl-methacrylate, is more difficult to treat than if there was no implant in the bone. Prophylactic internal fixation should usually be followed by radiotherapy to inhibit further tumor growth and bone destruction. It is easier to stabilize a bone while it is still intact and rehabilitation and convalescence are shorter and easier. Depending on the primary lesion, endocrine treatment or chemotherapy may also be necessary. Providing the lesion is irradiated, there is no evidence to suggest that surgery increases the risk of disseminating tumor cells either locally or into the circulation. If the patient is not fit for surgery, then radiotherapy and nonweight-bearing is indicated.

Pathological fractures are not necessarily a manifestation of terminal disease, and primary internal stabilization followed by radiotherapy is usually the treatment of choice, and certainly the only modality likely to restore mobility as well as relieve pain. Untreated pathological fractures rarely heal, and although radiotherapy may achieve local tumor control, bony union remains unlikely. Radiotherapy inhibits chondrogenesis, a prerequisite for fracture healing, and with large areas of bone destruction there may be insufficient matrix remaining for adequate repair.

The development of back pain in a patient with cancer, associated with an abnormality on a plain spinal radiograph, should serve as a warning for the possible development of spinal cord compression. In this situation more than 60% of patients will have myelographic abnormalities or evidence of epidural disease on magnetic resonance imaging. The key to successful rehabilitation is early diagnosis, high-dose corticosteroids, rapid assessment, and urgent referral for both decompression and spinal stabilization or radiotherapy. Neurological recovery is unlikely if the spinal compression is not relieved within 24-48 h.

Spinal instability is a cause of back pain in approximately 10% of patients with metastatic bone disease. This can cause excruciating pain, which is mechanical in origin. The patient is only comfortable when lying absolutely still and any movement reproduces severe pain. Consequently, the patient may not be able to sit, stand or walk even with the use of a spinal support. Because the pain is due to the instability, radiotherapy or systemic treatment will not relieve the pain. As with a pathological long-bone fracture, stabilization is required for pain relief. This involves major surgery, which may be associated with significant morbidity and mortality. There are several methods of spinal stabilization, but the posterior approach is technically easier and allows stabilization of a longer length of the spine. With careful selection of patients, excellent results can be obtained [8].

**Bisphosphonates**

All bisphosphonates are characterized by a phosphorus-carbon-phosphorus (P-C-P)-containing central structure, which promotes their binding to the mineralized bone matrix, and a variable R’ chain which determines the relative potency, side effects, and probably also the precise mechanism of action. Following administration, bisphosphonates bind avidly to exposed bone mineral around resorbing osteoclasts leading to very high local concentrations of bisphosphonate in the resorption lacunae (up to 1,000 µM). On release from the bone surface, bisphosphonates are internalized by the osteoclast, where they cause disruption of the biochemical processes involved in bone resorption [9].

Bisphosphonates also cause osteoclast apoptosis, with the appearance of distinctive changes in cell and nuclear morphology. Although the molecular targets responsible for promoting this apoptosis are unknown, the bisphosphonates have recently been shown to inhibit enzymes of the mevalonate pathway which are ultimately responsible for events that lead to the post-translational modification of GTP-binding proteins such as Ras. Recent studies also suggest that bisphosphonates may have direct apoptotic effects on tumor cells [10, 11].

**Clinical Uses of Bisphosphonates**

**Bisphosphonates for Hypercalcemia of Malignancy**

Hypercalcemia is the most common metabolic complication of malignancy producing many unpleasant gastrointestinal and neurological symptoms. Focal osteolysis by tumor cells, generalized osteolysis by humoral factors secreted by the tumor, increased renal tubular reabsorption of calcium and impaired renal glomerular function may all contribute to the pathophysiology. Intravenous bisphosphonates, in conjunction with rehydration, are now established as the treatment of choice for hypercalcemia. Seventy to ninety percent of patients will achieve normocalcemia resulting in relief of symptoms and improved quality of life [12].
Bisphosphonates for Bone Pain

Radiotherapy remains the treatment of choice for localized bone pain but many patients have widespread poorly localized, nonmechanical bone pain while others will experience recurrence of pain in previously irradiated skeletal sites. The bisphosphonates provide an alternative treatment approach to the management of these patients.

Most experience with bisphosphonates for bone pain is from their use for skeletal metastases from advanced breast cancer. The majority of early studies were open uncontrolled studies, but subsequent randomized controlled trials of intravenous pamidronate, clodronate, ibandronate, and zoledronate have all demonstrated useful pain relief [13-15]. To obtain optimal effects, the intravenous route is necessary, at least until more potent and well-tolerated oral bisphosphonates have been developed. It has not been convincingly demonstrated that any of the currently available oral bisphosphonates, in the absence of systemic anticancer treatment, can significantly reduce metastatic bone pain [13].

The effect of bisphosphonates on pain seems to be independent of the nature of the underlying tumor or radiographic appearance of the metastases, with sclerotic lesions responding similarly to lytic metastases. Additionally, there appears to be an important link between metastatic bone pain and the rate of bone resorption, with subjective response correlating with biochemical response [16]. The aim of bisphosphonate treatment should be to restore the rate of bone resorption to normal. With the currently available bisphosphonates, patients with bone metastases and a very high rate of bone resorption respond poorly. Monitoring of bone markers is likely to become an important tool in evaluating the benefits of bisphosphonates [17].

Bisphosphonates as Adjunctive Therapy in Metastatic Bone Disease

The potential value of bisphosphonates in metastatic bone disease was first appreciated in the early 1980s. Several small pilot studies encouraged investigators to evaluate either regular intravenous infusions of pamidronate, enteric-coated oral pamidronate, or either oral or parenteral clodronate in advanced breast cancer [18]. In addition to the effects on bone pain, sclerosis of lytic lesions was seen in phase II studies of intravenous pamidronate in the absence of specific anticancer treatments. Subsequently a reduction in skeletal morbidity was reported in the randomized studies of oral clodronate in advanced breast cancer and multiple myeloma (Table 1) [19-21].

Subsequently other randomized trials were performed, including two studies in advanced breast cancer comparing chemotherapy plus intravenous pamidronate with chemotherapy alone [22, 23]. These studies both reported a significant improvement in time to progression in bone in favor of combination therapy. They were followed by large placebo-controlled studies of pamidronate in advanced breast cancer and multiple myeloma given monthly at a dose of 90 mg by intravenous infusion in addition to appropriate endocrine or cytotoxic systemic treatments [2, 3, 24]. These trials showed that pamidronate significantly reduced skeletal morbidity in both advanced breast cancer and multiple myeloma and led to worldwide registration of pamidronate. Differences in skeletal morbidity began to show after three months of treatment and were maintained throughout the two-year study period. In addition, in the pamidronate-treated patients, quality of life was maintained and a reduction in pain and analgesic use was observed in comparison to the placebo group.

The evidence of clinical benefit from pamidronate in breast cancer and multiple myeloma is now overwhelming. Attention is now concentrated on trying to define the best time to start treatment, the optimum duration of treatment and prediction of those patients most likely to benefit. Biochemical response also seems to predict for the likelihood of skeletal events, with those patients failing to normalize their bone resorption rate on bisphosphonates experiencing a higher skeletal morbidity rate than those achieving normal bone markers [25]. No significant overall effects on survival have yet been seen, although subgroup analyses have suggested that young (<50 years) patients with breast cancer and myeloma patients receiving salvage chemotherapy may gain a small survival advantage [1, 26].

We are still lacking good data from randomized trials of the role of bisphosphonates for other tumor types affecting bone. Osteoclast stimulation is a consistent finding in all tumor types, even those associated with predominantly sclerotic metastases, and certainly acute pain relief is seen in prostate cancer. However, at the present time long-term bisphosphonate use cannot be justified outside clinical trials until more evidence from the current trials is available.

New Bisphosphonates

At present clodronate, usually given orally, and infusions of pamidronate are the two most widely used bisphosphonates in oncology. However, a small percentage (<5%) of an oral dose of clodronate is absorbed (Fig. 2), and for some patients the size and number of capsules required limit compliance, while infusions of pamidronate are costly, time-consuming and place additional demands on already overworked intravenous therapy units. The development of more potent bisphosphonates could be expected to simplify treatment and possibly improve the therapeutic effectiveness of bisphosphonate therapy.

Zoledronate is the most potent bisphosphonate in clinical development, and in vitro systems has around 100-1,000
times the potency of pamidronate. A phase I study in 30 patients with hypercalcemia indicated dose levels as low as 0.02 mg/kg (1-2 mg total dose) were effective in achieving normocalcemia [27], and a randomized comparison with pamidronate in hypercalcemia has now been completed. This has shown more rapid and complete control of hypercalcemia with zoledronate at doses of 4-8 mg [28].

In normocalcemic patients receiving zoledronate, a dose-dependent reduction in deoxypyridinoline, a specific marker of bone resorption, was identified. These biochemical responses were at least as large as those previously reported after infusions of pamidronate 90 mg, and pain relief was impressive, particularly at the highest dose of 8 mg [15].

Recently, a randomized double-blind, dose-finding phase II study of zoledronate has been completed for the treatment of osteolytic metastases from breast cancer and multiple myeloma, which defined a dose of 4-8 mg of zoledronate as appropriate for phase III evaluation across the spectrum of metastatic bone disease. Recruitment is now complete and results from these studies are expected next year.
Ibandronate is another highly potent amino-bisphosphonate which is licensed in Europe for the treatment of hypercalcemia of malignancy, and in late clinical development for both the treatment of metastatic bone disease, and the prevention and treatment of osteoporosis. Preliminary analysis of a phase III placebo-controlled trial of monthly infusions in breast cancer has shown a significant reduction in skeletal-related morbidity with ibandronate 4 mg [14]. Additionally, a film-coated tablet has been developed which has been shown to produce a dose-dependent reduction, at doses that are generally well tolerated, in both urinary calcium and collagen croslink excretion [29]. Further development of this oral formulation is anticipated.

**Bisphosphonates for Maintenance of Skeletal Health**

**The Normal Skeleton**

Many patients with cancer are at increased risk of osteoporosis because of the endocrine changes induced by cancer treatments. This is a particularly important long-term problem in women with breast cancer for whom there are concerns about the safety of hormone replacement therapy. Osteoporosis can be both prevented and treated effectively with bisphosphonates [30] and their use should be seriously considered in women experiencing a premature menopause.

**Prevention of Bone Metastases**

In addition to the well-recognized release of bone cell-activating factors from the tumor, it is now appreciated that release of bone-derived growth factors and cytokines from resorbing bone can both attract cancer cells to the bone surface and facilitate their growth and proliferation [10, 11]. Inhibition of bone resorption could therefore have an effect on the development and progression of metastatic bone disease. There are numerous animal studies indicating that bisphosphonates can prevent the development of metastatic bone disease, and a number of clinical studies with the bisphosphonate clodronate suggest that the promising results in animals do translate into the human situation, although conflicting results have recently been reported. Powles *et al.* have reported a reduction in the development of bone metastases in a study of 1,079 women with primary operable breast cancer. After a median follow-up of around four years, only 28 (5.2%) patients on clodronate had developed definite bone metastases compared with 44 (8.1%) on placebo (p = 0.054) [31].

Diel *et al.* reported a study of 302 patients without overt evidence of metastatic disease, but selected on the basis of breast cancer cells in the bone marrow identified by immunocytochemistry, who were randomized to receive oral clodronate or allocated to a control group. After a median follow-up of 36 months, those randomized to clodronate had a reduced incidence of bone metastases (11 versus 25, p = < .002) and, most surprisingly, a reduction in extraskeletal metastases (19 versus 42, p = < .001) as well [32]. The effects on extraskeletal metastases are difficult to explain but suggest that, in these patients with “in transit” micrometastases, the growth factors and cytokines normally released from bone are necessary for tumor cell survival and/or their biological capability to establish a metastatic focus. However, a very similar sized study of 299 women receiving adjuvant systemic treatment with or without oral clodronate, has produced conflicting results and should temper enthusiasm outside the clinical trial setting. In this study from Scandinavia [33], a higher incidence of both bone and extraskeletal metastases occurred and both disease-free (52% versus 69%) and overall (68% versus 81%) five-year survival figures were significantly worse in the clodronate-treated patients.

Identifying a definite adjuvant role for bisphosphonates will require further very large randomized trials. These are about to commence with zoledronate, clodronate and ibandronate, respectively. A positive study, coupled with the known positive effects of bisphosphonates on bone mass, would make routine prescription of adjuvant bisphosphonate treatment a very high priority. However, until the completion of confirmatory studies, the adjuvant use of bisphosphonates cannot be recommended except for the prevention or treatment of osteoporosis.

**Other Osteoclast Inhibitors**

In recent years much has been learned about the signaling mechanisms between osteoblasts and osteoclasts and the control of bone metabolism in cancer. Osteoprotegerin (OPG) is a member of the tumor necrosis factor receptor superfamily which is a natural inhibitor of osteoclast production and activity (Fig. 3). OPG acts as a decoy receptor binding with OPG-ligand, the natural stimulator of osteoclast maturation that is produced in large quantities by the osteoblast [34]. OPG has recently been shown to inhibit cancer-induced bone destruction and reduce skeletal pain in mice [35], and a synthetic version is now entering phase I trials in cancer patients. If the effects on bone resorption that have been seen in normal volunteer testing (Amgen—data on file) are confirmed in a cancer population, this long-acting subcutaneous preparation could be of great importance in the future.

**Conclusions and Recommendations**

The opportunities for improving the management of metastatic bone disease have never been greater. Recent
developments have occurred in all aspects of cancer management with improvements in skeletal imaging, reconstructive orthopedic surgery, and radiotherapy—particularly through the development of bone-seeking radiopharmaceuticals, new endocrine and cytotoxic treatments, and an increasing use of bisphosphonates to prevent and treat skeletal complications.

The bisphosphonates are an important class of agents for the treatment of metastatic bone disease. In addition to their confirmed status as the treatment of choice for hypercalcemia of malignancy, randomized controlled trials have clearly demonstrated that long-term bisphosphonate treatment is effective in reducing skeletal morbidity in breast cancer with fewer skeletal-related events, reduced pain and analgesic consumption, and improved quality of life. As a result, bisphosphonates should now be part of the routine management of metastatic bone disease from breast cancer and multiple myeloma. Further data are required to define their role in the routine management of metastatic bone disease from other tumors (Table 2).

The optimum time in the course of the disease to start bisphosphonates remains uncertain, but once treatment is initiated, patients should continue to receive bisphosphonate treatment for as long as the skeleton is the dominant site of metastases.

Bisphosphonates may also prevent, or at least delay, the development of skeletal metastases and will prevent treatment-induced osteoporosis, but their routine use in early breast cancer cannot be recommended until the completion of confirmatory trials.

ACKNOWLEDGMENT

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Table 2. Confirmed and unconfirmed indications for bisphosphonates in oncology

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