The use of bisphosphonates in skeletal disease due to breast cancer

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ABSTRACT
The variability of different breast cancers in the susceptibility to metastatic bone disease is poorly understood, but may depend in part upon gene expression of PTHrP and the vitamin D receptor. In contrast, much more is known of the manner which metastatic breast disease affects bone remodelling to induce osteolytic bone disease. Mechanisms include a generalised increase in activation frequency at sites close to metastatic tissue, an imbalance between the amount of bone formed and that resorbed within resorption cavities, and uncoupling of bone formation from bone resorption. The greatest morbidity from metastatic bone disease arises from osteolytic disease and gives rise to hypercalcemia, bone pain and fractures. Since osteolysis is primarily mediated by the activation of osteoclasts, there has been a great deal of interest in the use of agents which primarily affect bone pain and fractures. Since osteolysis is primarily mediated by the activation of osteoclasts, there has been a great deal of interest in the use of agents which primarily affect bone metabolism to alter the natural history of metastatic bone disease. Non-steroidal anti-inflammatory agents and cytotoxic agents are capable of inducing responses in bone, but are limited by their toxicity when effective doses are utilized. The use of calcitonin in the long term suppression of osteolysis has also been disappointing. The bisphosphonates are, however, capable of inducing sustained decreases in osteoclast activity and numbers in patients with osteolytic bone disease. There are now several studies which have examined the effects of the bisphosphonates on skeletal morbidity in breast cancer. Both clodronate and pamidronate decrease the incidence of hypercalcemia, bone pain and pathological fractures, but do not significantly alter mortality. Given, however, the unchanged survival in patients with metastatic bone disease, significant improvements in the quality of remaining life is an important therapeutic effect.

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Neoplasia is commonly associated with skeletal complications and disturbances in calcium homeostasis. Bone pain, pathological fracture and hypercalcemia account collectively for a large part of morbidity and some of the mortality associated with these complications. They most frequently occur in patients with focal osteolytic metastases. Generalized skeletal disease may also arise in myeloma and in solid tumors from the endocrine consequences of neoplasia. There is presently still a great deal of uncertainty as to the mechanisms for the seeding and growth of neoplastic cells within the skeleton, but a lot is now known concerning the consequences of this on bone remodelling. Mechanisms for bone destruction. Tumor mediated bone disease has been characteristically divided into focal bone disease associated with metastases and generalized bone disease, for example in myelomatosis. In turn, metastatic disease is often characterised as osteolytic or osteosclerotic. In practice the distinction is not straightforward since the features are commonly associated. In all these contexts, however, bone disease arises from three principal disturbances in the bone remodelling sequence.

Increased turnover. In metastatic bone disease there is evidence for increased resorption, but also both biochemical and histomorphometric evidence for increased bone formation suggesting that all the elements of bone turnover are increased (Fig. 1). An increase in bone turnover alone decreases skeletal mass since resorption precedes formation. A 5-fold increase in bone turnover will decrease bone mass by about 20% at cancellous bone sites.

Imbalance. Secondly, the amount of bone deposited in a resorption cavity may not equal the volume of bone removed. This leads to skeletal imbalance without necessarily implying a disorder of coupling. Skeletal imbalance contributes to bone loss that occurs in myeloma and the generalized increase in bone resorption found with some solid tumors. When bone turnover is increased this accelerates skeletal losses. The reason why imbalance occurs at remodelling sites is not known.

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Table 1 - Responses of 72 patients with hypercalcemia to 1500mg clodronate according to tumor type. All patients were refractory to saline alone and none received concomitant treatment.¹

<table>
<thead>
<tr>
<th>Patients becoming normocalcemic</th>
<th>Number of treatments</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral hypercalcemia*</td>
<td>25</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Skeletal metastases</td>
<td>30</td>
<td>22</td>
<td>73</td>
</tr>
<tr>
<td>Myelomatosis</td>
<td>17</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>All patients</td>
<td>72</td>
<td>51</td>
<td>71</td>
</tr>
</tbody>
</table>

*No radiographic evidence of skeletal metastases.

Possible mediators include decreased circulating levels of parathyroid hormone and calcitriol which have trophic effects on osteoblasts. Inhibitors of bone resorption, including chemotherapy, bisphosphonates and mithramycin (plicamycin), increase circulating levels of calcitriol and alkaline phosphatase where given to hypercalcemic patients, suggesting a decrease in the inhibition of osteoblast activity.² Also, the production of cytokines such as TNF and interleukins may directly suppress osteoblastic activity.⁶

Uncoupling. High tumor cell burdens are associated with a lack of coupling in that bone resorption occurs but is not the subsequent site for new bone formation. This in turn accelerates skeletal losses. Repeated waves of bone resorption without repair leads to the destruction of bone architecture and osteolytic foci. Osteosclerotic metastases are commonly due to uncoupled bone formation - namely the deposition of new bone, not at sites of prior bone resorption, but on quiescent bone surfaces or arising from stromal condensations within the marrow cavity. As in the case of osteolytic disease bone formation is mediated by osteoblasts rather than directly by tumor cells. Most sclerotic lesions are mixed lesions where uncoupled bone resorption and formation are occurring together but at different sites. Conversely many osteolytic lesions seen radiographically are mixed lesions where uncoupled osteolysis predominates.⁷

Determinations of skeletal disease and osteoclast activation. Skeletal metastases. Bone appears to be a preferential site for metastases for some cancers but not for others. For example, skeletal disease will affect more than 70 percent of women with breast cancer but only 5 percent of patients with gastric cancer. It is possible, however, that this reflects only the length of disease between diagnosis and death rather than differences in predilection for skeletal sites. Predictors of skeletal disease in breast cancer include estrogen receptor status. Tumors expressing high concentrations of estrogen receptors are more likely to metastasize to skeletal rather than soft tissue sites. Receptor status is, however, not a predictor of metastatic disease itself. A variety of other factors have been examined including circulating glycoproteins, fetal proteins, indices of proliferation and the presence of cancer cells in marrow. They predict metastatic disease with various degrees of accuracy, but have little or no discriminatory value for the likelihood of skeletal disease. The expression of parathyroid hormone related protein (PTHrP) is more common in skeletal metastases than in soft tissue metastases. The same distribution is found, however, in patients with both types of metastases where the primary tumor does not express PTHrP, suggesting that PTHrP expression occurs after the metastatic event. Since there is also no relationship between ER receptor status and PTHrP expression, these observations suggest that PTHrP expression occurs preferentially in the skeletal environment.

The attachment of tumor cells to distant sites may be related to increased numbers of laminin receptors which are important for attachment to basement membrane collagens. Laminin antagonists have been shown to inhibit the formation of osteolytic metastases of melanoma cells in nude mice whereas laminin potentiates the process.⁸ The effect is unlikely to be skeletal specific, since these agents have similar effects on pulmonary metastases. Other proteins affecting cell adhesion include the glycoprotein E-cadherin, and its expression in breast cancer cells is associated with decreased numbers of skeletal metastases.⁹

Osteoclast activation. Increased numbers of osteoclasts are frequently observed in close proximity to tumor cells in histological specimens obtained from patients with solid tumors.⁴ The mechanism for osteoclast activation differs among different tumor types. More is known about the mechanisms for osteoclast activation in myeloma than in solid tumors. At least 3 cytokines have been identified as activators of bone resorption including tumor necrosis factor β (TNF-β) or lymphotoxin, interleukin-1 (IL-1) and IL-6.¹⁰ Candidates for osteoclast activation in breast cancer include prostaglandins, procathepsin D tumor necrosing factor, PTHrP and the transforming growth factors.¹⁰ Most histological evidence would suggest that increased bone resorption can be accounted for in breast cancer by the increased numbers of osteoclasts,¹³ but it is possible that bone resorption mediated by tumor cells may supervene in the late stages of the disorder. PTHrP is expressed by tumor tissue and has been localized in many squamous cell cancers, particularly of the lung and breast. High PTHrP values are also seen in some patients with renal cell carcinoma, transitional cell and liver carcinoma, all of which may be associated with humoral hypercalcemia in the absence of skeletal...
metastases. The division of hypercalcemia patients with solid tumors according to the presence or absence of metastatic bone disease is an oversimplification in patients with breast cancer since humoral mechanisms increasing bone resorption and renal tubular reabsorption of calcium are also found in patients with evidence of metastatic bone disease.

**Consequences of bone destruction.** The most frequent sites of involvement are the vertebrae, pelvis, ribs, femur and skull. Patients with skeletal disease without soft tissue disease commonly have a prolonged survival but a high degree of morbidity. The major morbidity is bone pain, fracture, paraplegia often associated with fracture, and hypercalcemia.12

**Hypercalcemia.** Hypercalcemia will complicate approximately 30-40% of patients with breast cancer, 20% of patients with lung cancer and more rarely in other tumor types. The median survival in patients with solid tumors is 1 or 2 months, and 70-80% are dead within 1 year. Carcinoma of the breast, bronchus and bladder account for approximately half the cases of hypercalcemia in patients with solid tumors. Whereas the induction of hypercalcemia is almost invariably related to osteoclast activation of bone resorption, its maintenance is complex and involves changes at other major sites for calcium exchange to and from the extracellular fluid.11 Some of these changes offset the hypercalcemic challenge of increased bone resorption, whereas others aggravate this. In addition, a variety of tumors, particularly those inducing humoral hypercalcemia, appear to secrete factors including PTHrP that increase renal tubular reabsorption of calcium. In some patients, increased renal tubular reabsorption is the mechanism for the maintenance of hypercalcemia.11

**Bone pain.** Bone pain is extremely common. Fifty percent of all cancer pain is due to skeletal metastases and approximately 70% of patients with breast cancer metastatic to bone will have bone pain during their remaining lifetime. The most common sites of pain are the spine and the chest although pain around the shoulder girdle and hip are also frequent. Pain is not invariably associated with osteolytic foci nor with fracture. Adequate analgesia is often impossible without the use of opiates. Although radiotherapy may be useful for localised lesions, there are limitations in its repeated use, with widespread sites of involvement, and pain which is migratory.

**Fractures.** The most common fracture is vertebral fracture which gives rise to bone pain, kyphosis, loss of height and occasionally paraplegia. Approximately 50% of women with metastatic breast cancer have vertebral fractures.12 Other common sites of fracture are the ribs and the proximal ends of humerus and femur but their frequency is much lower, about one-third of the rate of spinal fractures. The risk of pathological fractures in long bones correlates with the degree of cortical destruction and rises markedly when more than 50 percent of the cortex is destroyed. Fractures of the appendicular skeleton may be very difficult to treat because the surrounding bone may be grossly abnormal making fixation difficult and fracture healing may be impaired.

**Approaches to management.** Irrespective of whether focal or generalized osteolysis occurs, the pathogenesis for increased bone resorption in breast cancer involves the activation of osteoclasts. This has prompted the evaluation of agents which act on bone metabolism rather than on tumor metabolism in the hope that they might alter the expression of neoplasia on bone. Agents evaluated include mithramycin, cis-platin, gallium nitrate, prostaglandin synthetase inhibitors such as aspirin, the calcitonins and bisphosphonates. The bisphosphonates appear to have the greatest potential. In tissue culture they inhibit normal and stimulated bone resorption and prevent osteolysis due to parathyroid hormone,12-20(2)(OH), D3, prostaglandins and lymphokines. They also prevent, at least in part, the loss of bone due to experimental tumors.13 In man, they are capable of inhibiting osteoclast-mediated bone resorption over long periods without significant systemic toxicity.13,14 Of the various bisphosphonates tested in this context, the greatest amount of work has been undertaken with clodronate and pamidronate, but several other bisphosphonates are being tested. The uptake of these bisphosphonates by the skeleton is not uniform. Uptake appears to be dependent in part on bone blood flow, but is particularly marked at sites of active bone remodelling. The patchy distribution at sites of disease activity has important therapeutic implications since a proportionately greater dose is delivered to the site of the disorder than elsewhere. This targeting effect may have obvious pharmacological advantages in sparing non-affected

| Table 2 - Trial outcomes in 173 patients with breast cancer and skeletal metastases given clodronate 1600mg daily or placebo. From Paterson et al, 1993.12 |
|---------------------------------|-----------------|-----------------|
|                                 | Clodronate      | Placebo         |
| **Number of patients**          | 85              | 88              |
| **Deaths**                      | 58              | 66              |
| **Hypercalcemic episodes**      | 28              | 51              |
| **Terminal episodes of hypercalcemia** | 7                | 17              |
| **Hypercalciuria**              | 32              | 20              |
| **Hypocalciemia**               | 6               | 2               |
| **Vertebral fracture (/100 pt years)** | 84              | 124             |
| **Patients requiring radiotherapy** | 1               | 1               |
| **All morbid events**           | 219             | 305             |
| **Survival at 1 year**          | 62              | 54              |
| **at 2 years**                  | 35              | 14              |
Table 3 - Incidence of complications in 34 patients with breast cancer and skeletal metastases given clodronate or placebo for 1 year and followed up for a further year. From Elomaa et al, 1987,26

<table>
<thead>
<tr>
<th></th>
<th>Clodronate</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>1 year 2 year total</td>
<td>1 year 2 year total</td>
</tr>
<tr>
<td>New bone metastases</td>
<td>3 11 14 11 11 14</td>
<td>1 1 2 4 1 2</td>
</tr>
<tr>
<td>Skeletal fractures</td>
<td>1 1 2 4 1 2 2</td>
<td>1 1 2 4 1 2 2</td>
</tr>
<tr>
<td>Episodes of hypercalcemia</td>
<td>14 11 11 9 11 11</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td></td>
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</tbody>
</table>

sites.

**Treatment of hypercalcemia.** Etidronate, clodronate and pamidronate have been the most extensively tested bisphosphonates in hypercalcemia. There are now many reports showing that these agents decrease serum calcium in the majority of patients. The most frequently used regimens have been intravenous infusions for several days which lower serum calcium to normal in about 80-90% of patients. However, a single infusion has comparable effects as the same total dose infused for several days.14,11 The rate of response to intravenous bisphosphonates is slow and it takes 1-2 days before a response is observed. Maximal effects are observed after 4-7 days. This contrasts with the use of calcitonin where effects may be observed within 1-2 hours, but are not long-lasting. In clinical practice this slow response is masked since concurrent rehydration is normally given. In the absence of further treatment hypercalcemia recurs within several weeks. The calcium-lowering effect is attributable to the inhibition of bone resorption. In some patients serum calcium is not restored to normal due to concurrently increased renal tubular reabsorption of calcium (Table 1), an effect of PTHrP not reversed by bisphosphonates. There have been several comparative studies of different bisphosphonates. The results of treatment with clodronate and pamidronate are consistently greater than the effects of etidronate.1 One study has compared pamidronate with clodronate and showed a more complete effect of pamidronate,16 but a sub-optimal dose of clodronate was used.

**Treatment of bone pain.** Both pamidronate and clodronate have been shown to decrease bone pain in placebo-controlled studies.17,18 Although the mechanism of skeletal pain in bone disease is not known, it is of interest that the response in bone pain is relatively slow and mirrors that of bone resorption. In addition a dose-dependent effect is seen,19 and suggests that the response may be related to a decrease in bone blood flow or to the inhibition of bone resorption. Improvement in pain due to neoplasia is also reported with calcitonin which has a much more rapid onset of action, both for the relief of symptoms and for the inhibition of bone resorption. The activity of calcitonin on pain may be due to the release of β-endorphins but circulating β-endorphins do not change following treatment with clodronate.20

**Prevention.** Whereas hormone and chemotherapy can achieve remission in many tumors, bone disease once established is often progressive. There is now good evidence that responses to both clodronate and

![Figure 1](image-url) - Histological findings in bone in normal women (control) and in women with breast cancer biopsied at sites distant, adjacent or within skeletal metastases. Note the increase in the eroded (ES/BS) and osteoclast surface (N.Oc/BS), the osteoblast surface (N.Ob/BaS) and bone formation rate (BFR) at all sites, but particularly adjacent or within metastases, From Taube et al, 1994,7 [95Ca178].
pamidronate can be induced and maintained on a long-term basis.\textsuperscript{3,21} The oral route of administration is more convenient than its intermittent intravenous injection, which is a requirement with pamidronate. The other widely available bisphosphonate, etidronate, is available as an oral formulation, but the doses required for long-term use impair the mineralization of bone. Indeed, its long-term use has shown no significant benefit in myelomatosi.\textsuperscript{22} In contrast, long-term treatment with clodronate and pamidronate have long-term effects on skeletal metabolism in patients with cancer affecting the skeleton. Biochemical indices of increased bone resorption are decreased for the duration of exposure to these agents. In the case of clodronate, osteoclast numbers are reduced to normal in breast cancer (Fig. 2). Moreover, the bone formation rate is not suppressed abnormally low. The long-term effects of these agents suggest that they might prevent or ameliorate the development of skeletal complications and there is some evidence for this view. The incidence of hypercalcemia is relatively low and this demands long-term or large randomized controlled studies. These have shown a 50% decrease in the incidence of hypercalcemia using either clodronate or pamidronate (Table 2).\textsuperscript{12,23} Several double blind studies suggest that long-term use of bisphosphonates are associated with a decrease in the incidence of bone pain or analgesic consumption.\textsuperscript{24,12} In the largest of these, patients with breast cancer were treated with clodronate 1600mg for up to 3 years, and bone pain was assessed by the requirements for radiotherapy to bone. Overall, there was a 30% reduction in requirements (Table 2), but this fell short of significance. As might be expected, open studies show a somewhat larger effect on bone pain and on the requirements for further radiotherapy.\textsuperscript{25}

The effects of bisphosphonates on fractures have been studied in patients with breast cancer. Vertebral fracture rates in women at the time of relapse are high, and treatment with clodronate or pamidronate significantly decreased the vertebral fracture rate (Table 2).\textsuperscript{23,26} Placebo controlled trials have shown similar effects on appendicular fractures.\textsuperscript{26} Several reports suggest that clodronate decreases the growth of existing lesions and indeed may reduce the formation of new lesions.\textsuperscript{26,27} In one study in breast cancer\textsuperscript{26} new bone metastases were observed in 3 of 17 clodronate treated patients, but in 11 of 17 placebo treated patients (Table 3). Unlike the effects on hypercalcemia and fracture, the effect disappeared shortly after stopping treatment. There are several reports of the induction of osteosclerosis following the treatment of patients with osteolytic lesions. It is probable that this represents continued uncoupled bone formation, rather than true healing of osteolytic disease. In a small double study of 34 patients with breast cancer, a significant survival advantage was shown in the treatment wing (Table 3). These patients were selected for treatment on the basis of severe skeletal disease, and the apparent survival advantage was largely due to a decrease in hypercalcemia and orthopedic complications. As might be expected, a significant survival advantage has not been confirmed in larger studies using a more representative sample in breast cancer\textsuperscript{12} but, notwithstanding, small trends have been found, though much larger studies would be required to show a worthwhile effect with sufficient power.

Cost-benefit. Long-term treatment with bisphosphonates are associated with the prevention at least in part of the clinical complications of osteolytic disease. The extent of the effect varies between series but large double blind studies indicate an efficacy that ranges from 25 to 50% for the prevention of hypercalcemia, bone pain and pathological fracture. The question arises whether these dividends are worthwhile and if so whom and when to treat. For rare events, prophylaxis may not be beneficial. For example, the incidence of hypercalcemia in the first year of treatment in myelomatosi (excluding initial presentation) is less than 5/100 patient years, and treatment is likely to save at most 3 or 4 episodes for every 100 years of treatment. If the management of hypercalcemia were a major priority for treatment then treatment rather than prevention of intercurrent hypercalcemia may be

**Figure 2** - Effects of clodronate 1600mg daily, calcitonin 100IU daily or placebo on osteoclast numbers in 36 patients with metastatic breast cancer. Before treatment (hatched boxes), osteoclast numbers were increased. Clodronate treatment for 6 months induced a reduction in osteoclast surfaces and numbers (mean±SEM) to normal control values (open box). From Taube et al, 1993.\textsuperscript{13} [90C6246].
more worthwhile.

Different considerations may apply to the prevention of bone pain and fractures. The frequency, morbidity and costs of these events are high. In patients who have required a single course of radiotherapy for skeletal disease, the requirements for further radiotherapy are high, particularly in lung cancer and so too the lifetime risk of fracture. In breast cancer these lifetime risks are lower even though survival is longer. Surprisingly very few formal cost-benefit analyses have been undertaken. In women with breast cancer and metastatic skeletal disease, the skeletal disease accounts for the largest component of hospital costs and totals 63% of the budget. In such patients, even modest reductions in morbidity are economic, at least as judged by the costs of the US Healthcare system so that long-term treatment may be of cost benefit to patients with a wide variety of tumor types.

References


