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# Bisphosphonates in the Management of Breast Cancer

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*The use of bisphosphonates in the treatment of bone metastases from breast cancer improves palliation of potential symptoms. A benefit from adjuvant use is being studied.*

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**Background:** Bone is the most frequent site of metastasis in patients with breast cancer. Bone metastasis, particularly osteolytic bone destruction, is usually associated with significant morbidity and deterioration of quality of life. Bisphosphonates are specific inhibitors of osteoclast activity used in the treatment of hypercalcemia of malignancy and osteolytic bone disease.

**Methods:** We reviewed pertinent literature on the use of bisphosphonates therapy to treat metastatic breast cancer.

**Results:** The use of bisphosphonates in the management of osteolytic bone metastases results in improved palliation of symptoms. Use of these agents in the adjuvant setting may help to prevent bone metastases.

**Conclusions:** Bisphosphonates represent an effective palliative treatment when combined with chemotherapy and hormonal therapy for the management of osteolytic bone metastases. Identifying the exact mechanism of action requires further investigation to better define the possibility of a direct antitumor effect. The role of bisphosphonates in the adjuvant setting is still controversial, pending the results of large randomized trials.

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## Introduction

The skeleton is the most common site of recurrence of metastatic breast cancer, and bone metastasis will occur in 49% to 85% of patients with breast cancer during their lifetime.<sup>1,2</sup> The morbidity from bone metastases in patients with breast cancer represents a significant health problem, and the major clinical manifestation involves osteolytic bone destruction.<sup>2</sup> Depending on the extent of the disease and the site of metastasis, patients may be asymptomatic, may develop hypercalcemia, or may experience chronic, debilitating pain with a significant compromise in quality of life. In advanced cases, significant complications such as spinal cord compression or pathologic fracture of a long bone can result in permanent disabilities.

Tumor-induced osteolysis is essentially mediated by osteoclasts whose number and activity appear to be influenced by factors produced in the bone marrow microenvironment (osteoclast-stimulating factors) that act by a paracrine mechanism.<sup>3</sup> Bisphosphonates are specific inhibitors of osteoclastic activity and have been used for the treatment of hypercalcemia associated with malignancy.<sup>4</sup> The bisphosphonates are a family of pyrophosphate analogues that bind to bone hydroxyapatite and inhibit bone resorption locally. A 90-mg 2-hour monthly infusion of the bisphosphonate has been associated with reduced skeletal complications when used with chemotherapy or hormonal therapy in patients with osteolytic bone metastases.<sup>5,6</sup> Pamidronate has been approved by the Food and Drug Administration for the treatment of normocalcemic patients with myeloma-associated bone disease and osteolytic lesions of metastatic breast cancer.

## Biologic Mechanisms of the Bone Remodeling Process

The concomitant action of host components and mechanical factors has been identified as being responsible for the constant remodeling of bone. The host components include osteoblasts and osteoclasts (which are directly responsible for the active process of remodeling) and cytokines and other humoral factors (which act through a paracrine mechanism).<sup>7</sup>

Osteoblasts derived from hematogenous precursors produce collagen matrix as well as osteocalcin, osteopontin, and osteonectin, the bone-specific proteins. Osteoblasts are necessary for osteoclast activation and the functional dissolution of the bone. Osteoclasts, derived from the monocyte-macrophage cell line, are able to migrate and, when activated, dissolve the bone at attachment sites in disparate parts of the skeleton. They are influenced by a variety of cytokines, including macrophage colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, transforming growth factors (TGFs), and interleukin (IL)-6, most of which are produced by activated osteoblasts.<sup>8</sup>

In normal bone remodeling, the relationship between osteoblastic and osteolytic activity is balanced; this balance is termed "coupling." In pathologic or metabolic conditions such as metastatic disease or osteoporosis, this equilibrium can be altered, with the activity of one of the two cell types becoming prevalent and resulting in defective bone formation.<sup>9</sup>

A variety of cytokines and tumor-derived proteins produced by breast cancer cells are capable of osteoclastic activation. Parathyroid hormone-related peptide (PTH-rP), TGF- $\alpha$ , TGF- $\beta$ , prostaglandin, IL-1, and IL-6 have been more extensively investigated and appear to be among the most important osteoclast activators in metastatic breast cancer. Among the various cytokines, extensive investigations have been conducted on the role of PTH-rP, a peptide isolated approximately 10 years ago that is responsible for the hypercalcemia associated with malignancy. Experimental data derived from a series of studies using MDA-231 breast cancer cells in a nude mouse model suggest that PTH-rP expression in breast carcinoma cells may enhance the progression of metastatic disease to the bone. Furthermore, an interesting interaction between TGF- $\beta$  seems to play a critical role in the regulation of osteoclastic bone resorption and PTH-rP expression and may facilitate the osteolytic process associated with breast cancer invasion.<sup>10</sup>

## Bisphosphonates and Their Mechanism of Action

Bisphosphonates are natural components that are characterized by a P-C-P bond in their structure that is responsible not only for their binding to mineralized bone matrix, but also for their inhibitory effects on bone resorption.<sup>11</sup> They possess a carbon substitution for the oxygen of the pyrophosphate molecule and are therefore resistant to enzymatic hydrolysis by endogenous bisphosphonates. All bisphosphonates have a high affinity for hydroxyapatite crystals in bone, thus stabilizing bone mineral and

Inhibiting its dissolution.

The precise mechanism of action of the bisphosphonates on bone cells and bone resorption is not completely clear. Bisphosphonates inhibit osteoclastic function in several ways, eg, by producing a direct toxic effect on the resorbing osteoclasts, by promoting apoptosis, or by inhibiting the differentiation of the osteoclasts into mature osteoclasts.<sup>12</sup>

Bisphosphonates inhibit bone resorption due to PTH, PTH-rP, corticosteroids, retinoids, prostaglandins, and a variety of cytokines. The relative potency of bisphosphonates depends on the unique chemical structure of their side chains (Table 1). Etidronate, a first-generation agent, is the least potent inhibitor of bone resorption among the clinically evaluated bisphosphonates.<sup>13</sup> Clodronate and pamidronate, which were extensively evaluated in patients with malignant diseases, have been determined to be more potent.<sup>11-14</sup> Clodronate is approximately 10 times more potent than etidronate, whereas pamidronate appears to be 10 times more potent than clodronate.<sup>15,16</sup> Alendronate, which has a four-carbon amino side chain, displays high potency (10 times that of clodronate) and effectively inhibits osteoclast bone resorption at doses that do not impair bone mineralization.<sup>17</sup>

**Table 1. — Antiresorption Potency of Various Bisphosphonates**

	Relative Potency
<b>First-Generation Agents:</b>	
Etidronate	1
Clodronate	10
Tiludronate	10
<b>Second-Generation Agents:</b>	
Pamidronate	100
Alendronate	1,000
<b>Third-Generation Agents:</b>	
Ibandronate	10,000
Zoledronate	20,000

Zoledronate and ibandronate represent third-generation agents. Clinical data have demonstrated that these agents have an antiresorption potency that is at least a thousandfold superior to the first-generation agents.<sup>18,19</sup> Clinical applications of these bisphosphonates include treating conditions associated with increased bone resorption, particularly osteolytic bone metastasis from breast cancer and multiple myeloma.<sup>20,21</sup> Tumor-induced hypercalcemia and Paget's disease of the bone have also been successfully managed with these agents.

Data from a series of preclinical studies performed on animals led to clinical trials of the use of bisphosphonates in the prevention of osteoporosis.

Since 1990, clinical trials using daily oral doses of alendronate in postmenopausal women with osteoporosis have been conducted in many centers. These studies demonstrated that daily treatment with alendronate progressively increases the bone mass in the spine, hip, and total body and reduces the incidence of vertebral complications (fractures and deformities) associated with severe osteoporosis in postmenopausal women.<sup>17</sup>

The toxicity of bisphosphonates is strictly related to the route of administration of these agents.<sup>11</sup> The bisphosphonates are better tolerated when administered by intravenous injections because their metabolism is exclusively through renal excretion. Renal dysfunction is the main toxicity. The renal toxicity associated with intravenous administration of bisphosphonates is rare and is closely related to the drug dose and the rate of infusion. The clinical introduction of newer agents may offer an advantageous solution in terms of dosing that can prevent these unwanted effects.<sup>18,19</sup>

Some agents are administered orally, which is associated with poor absorption (usually <1%) and significant gastrointestinal toxicity that may be as severe as esophagitis and esophageal ulcers.

## Bisphosphonates to Treat Breast Cancer

The occurrence of bone metastasis is a common event in the natural history of breast cancer. In fact, bone localization is the most frequent site of metastatic disease in patients with advanced breast cancer.

Cytotoxic chemotherapy or hormonal agents used systemically are the preferred forms of treatment, but they usually are associated with only temporary control of symptomatic disease. The ultimate prognosis in patients with metastatic breast cancer of the bone is generally poor, but a proportion of these patients may survive longer and thus require palliative treatment of the symptoms and complications related to their bone metastases.

Alternative palliative bone-directed therapies involve localized radiation therapy and radioactive bone-seeking agents (strontium-89 and samarium-153), which usually are used to prevent pathologic fractures and reduce pain.<sup>22-24</sup>

Because of their activity as inhibitors of osteoclastic bone resorption, bisphosphonates have been shown to be effective in the palliative treatment of women with osteolytic bone metastases. The two most popular agents, clodronate and pamidronate, have been extensively investigated in multicenter clinical trials performed in the last 10 years (Table 2). These agents have demonstrated efficacy in the management of malignancy-associated hypercalcemia, replacing other agents such as calcitonin, corticosteroids, and plicamycin. Their use in patients with metastatic breast cancer has been associated with a delay in the onset of skeletal-related events and with improvement in pain control and overall quality of life.<sup>25,26</sup>

**Table 2. — Randomized Clinical Trials of Bisphosphonates in Breast Cancer-Related Skeletal Disease**

Investigators	Number of Patients	Agent (Dose)	Bone Pain	Pathologic Fractures	HCM	Survival
Paterson et al <sup>27</sup>	173	Clodronate (1600 mg/day orally)	Improved	Reduced	Reduced	No benefit
van Holten-Verzantvoort et al <sup>25</sup>	161	Pamidronate (600 mg/300 mg/day orally)	Improved	Reduced	Reduced	No benefit

Hortobagyi et al <sup>28</sup>	751	Pamidronate (90 mg IV every 3-4 weeks)	Improved	Reduced	Reduced	No benefit
HCM = hypercalcemia of malignancy IV = intravenous administration						

A series of phase II studies demonstrated the activity of bisphosphonates used as single agents in controlling symptomatic osteolytic bone metastases and reducing bone pain. The symptomatic efficacy appeared to be dose dependent, particularly for the oral agents, because of their poor absorption. These interesting results prompted randomized clinical trials to evaluate the efficacy of the drugs in the management of osteolytic bone disease.

In the first study, Paterson et al<sup>27</sup> used a double-blind, randomized, placebo-controlled trial to investigate oral clodronate at a dose of 1,600 mg/day. A total of 173 patients with osteolytic metastatic breast cancer were enrolled, and 85 received clodronate. In those receiving clodronate, the rate of all morbid skeletal events — including vertebral fractures and deformities — was significantly reduced ( $P < 0.001$ ). No significant differences in survival or side effects were observed between these two groups.

In 1993, van Holten-Verzantvoort et al<sup>25</sup> published the results of a randomized study using oral pamidronate in osteolytic metastatic breast cancer. Eighty-one patients were treated with oral pamidronate; due to severe gastrointestinal toxicity, a starting dose of 600 mg/day used in 29 patients was reduced to 300 mg/day in 52 patients. When compared with 80 control patients, the occurrence of hypercalcemia, severe bone pain, and impending fracture decreased by 65%, 30%, and 50%, respectively. The effect was dose dependent; unfortunately, there was a 23% drop-out rate due to severe gastrointestinal toxicity.

Subsequent investigations have focused mainly on the intravenous administration of pamidronate as palliative treatment. The results of two combined prospective, placebo-controlled, randomized clinical trials of intravenous pamidronate in patients with osteolytic bone metastases have been recently published by Hortobagyi et al.<sup>28</sup> Women with stage IV breast carcinoma who were receiving cytotoxic chemotherapy (380 patients) or endocrine therapy (371 patients) and who had at least one lytic bone lesion were given either 90 mg of pamidronate during a 2-hour infusion monthly for two years or a placebo infusion. After the results of the two studies were pooled, data from 367 patients treated with pamidronate and 384 patients given placebo were available for analysis. The proportion of patients with any skeletal complications was significantly less in the pamidronate group than in the placebo group at 15, 18, 21, and 24 months ( $P < 0.001$ ). In particular, the skeletal morbidity rate (the number of complications per year) at 24 months was 2.4 for the pamidronate group and 3.7 for the placebo group ( $P = 0.001$ ). The median time to the first skeletal complication was 13.9 months in the pamidronate group and 7.0 months in the placebo group. The time of first fracture was increased from 12.8 to 25.2 months. Pain and analgesic use were also decreased among the pamidronate patients. There was no survival difference between the two groups. Furthermore, treatment with pamidronate did not prevent progression of disease in the bone compared with the placebo.<sup>29</sup> Interestingly, when the two studies were analyzed separately, the reduction in skeletal-related events appeared more evident in the group of patients receiving cytotoxic chemotherapy (65% vs 46% for the placebo group) than for the group treated with hormone therapy (67% vs 56%). The reasons for the differences are not known at this time, but these results may suggest a synergistic antitumor effect between bisphosphonates and chemotherapy that requires further investigation.

Numerous attempts have been made in recent years to better define the biologic modifications associated with bisphosphonate activity, and a number of biochemical and serum protein markers have been proposed.<sup>30</sup> Excretion of alkaline phosphatase and urinary hydroxyproline has been considered to be a sensitive and specific marker for monitoring disease progression in bone metastasis.<sup>31</sup> Coleman et al<sup>32</sup> have reported the results of an evaluation of serum markers associated with bone resorption. N-telopeptide and c-telopeptide demonstrated the greatest variations in inhibition by bisphosphonates. Considering the low specificity and sensitivity of the present markers, none can be recommended for routine use in clinical practice. Future clinical trials may better define the role of these markers when used alone or in combination with others.

Once the efficacy of bisphosphonates as palliative treatment in metastatic breast cancer is established, the next logical step involves testing the possibility of preventing bone metastasis by using bisphosphonates.

Diel et al<sup>33</sup> recently reported a study involving 302 patients with primary breast cancer and tumor cells in the bone marrow. Patients were randomized to either clodronate treatment at a dose of 1,600 mg/day orally for two years (157 patients) or no therapy and standard follow-up (145 patients). All patients received standard adjuvant treatment. Analysis performed at 36 months of follow-up revealed that clodronate treatment was associated with a statistically significant reduction in the number of recurrences of

bone metastasis (12 vs 25 in the clodronate vs no treatment groups, respectively), visceral metastases (13 vs 27), and deaths (6 vs 22). In addition, the average number of bone metastases in clodronate-treated patients was significantly lower than that in the control group.

Preliminary data are now available on a randomized trial conducted by Powles et al,<sup>34</sup> which completed accrual in June 1997 and involved 1,079 patients with breast cancer. Patients were randomized to receive either clodronate 1,600 mg/day orally or placebo. Preliminary data suggest a reduction in bone metastases, particularly for postmenopausal patients. A longer follow-up period will be required to evaluate whether the incidence of bone metastases and eventually visceral metastases was reduced, as suggested by the intriguing results reported by Diel and colleagues.

## Future Directions

The use of bisphosphonates for the treatment of osteolytic lesions in the setting of metastatic breast cancer has steadily increased in the last several years. Randomized clinical trials have demonstrated a benefit, particularly for pamidronate-treated patients, with a significant reduction in skeletal-related complications and bone pain and an improvement in quality of life.

Based on these data, patients with osteolytic metastatic breast cancer should be initiated on bisphosphonate treatment as early as possible after diagnosis. Pamidronate given as an intravenous infusion every three or four weeks appears to be the most effective treatment and is associated with fewer side effects. This treatment should be continued for as long as efficacy is demonstrated. Oral bisphosphonates, particularly clodronate, may replace pamidronate with perhaps equivalent results but with less tolerance.

Future trials using a new generation of more potent bisphosphonates — zoledronate and ibandronate — may offer more effective palliative options and, when used in the setting of adjuvant treatment, are expected to clarify the role of this class of drugs in the prevention of bone metastasis in patients with breast cancer.

A phase I investigation of zoledronate has recently been completed. Doses of 4 mg and 8 mg given as a short infusion (5 minutes) were well tolerated.<sup>18</sup> Phase II trials are currently in progress. Markers of bone resorption will also be routinely evaluated in treated patients to evaluate the variation in clinical efficacy.

Many questions remain partially unanswered, including a detailed clarification of the molecular targets of bisphosphonates and the mechanism of action by which they affect osteoclast activity. Recent studies show that bisphosphonates promote apoptosis of osteoclasts, but they also can affect tumor cells.<sup>35,36</sup> In the setting of cancer, it is important to establish whether bisphosphonates have antitumor effects and which bisphosphonates are the most effective in this regard. No clinical data are presently available to suggest a possible role of bisphosphonates in the management of osteolytic bone metastases due to other solid tumors.

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