Tumor-induced osteolysis or lytic bone disease is mediated by osteoclast activation. Osteoclasts can be activated directly by products produced by tumors or indirectly through other nonmalignant cells. By reducing...
The bisphosphonates are eliminated almost exclusively through renal excretion. Significant nephrotoxicity can occur with these compounds, although this is clearly related to the drug dose and rate of infusion when given intravenously. Importantly, renal dysfunction results from the R1 group, so that more potent newer bisphosphonates with different R2 groups offer the opportunity for more convenient dosing schedules without significant nephrotoxicity.

Because bisphosphonates have high affinity for bone mineral, the drugs are highly concentrated in bone (approximately half of the intravenous dose). In addition, these drugs preferentially bind to bones that have high turnover rates. Thus, bisphosphonates are concentrated at the exposed bone surface, which is actively remodeling. They also bind more avidly with highly active trabecular bone than with cortical bone, which has a much lower bone turnover rate.

Once bisphosphonates become a part of bone that is not remodeling, they are biologically inactive. As a result, continued administration of these drugs is required to achieve the desired lasting inhibition of bone resorption.

**Bisphosphonate Treatment of Bone Metastases**

Because multiple myeloma and breast cancer are often accompanied by bone involvement with osteolytic bone destruction, most clinical trials of bisphosphonates have involved these two forms of cancer. However, recent trials are assessing the effects of bisphosphonates in treating bone metastases from other cancers, such as carcinoma of the prostate.

**Multiple Myeloma**

Multiple myeloma is characterized by the accumulation of terminally differentiated plasma cells in the bone marrow, and is accompanied by a marked increase in osteoclast activity and proliferation. This increase in osteoclast activity is mediated by the release of osteoclast-stimulating factors.[3,4] These factors are produced locally in the bone marrow microenvironment by cells of both tumor and nontumor origin.

Bone pain, the major clinical manifestation of multiple myeloma, is related to osteolytic bone destruction. Even patients who respond to chemotherapy may exhibit progression of skeletal disease.[5,6]

Although early studies of bisphosphonates in patients with myeloma suggested a reduction in bone pain and healing of lytic lesions, the trials involved few patients and were open-label in design.[7-9] Six large randomized trials of long-term bisphosphonate therapy have now been published; these involved the use of either the first-generation bisphosphonates etidronate or clodronate or the second-generation aminobisphosphonate pamidronate (Aredia).[5,10-14]

**Etidronate**—In a Canadian study of etidronate,[5] 173 newly diagnosed patients were entered, and 166 patients were randomized. All patients received intermittent oral melphalan (Alkeran) and prednisone as primary chemotherapy. Patients were then randomized to receive either daily oral etidronate (5 mg/kg) or placebo until death or termination of treatment due to side effects.

Although significant height loss occurred in both placebo- and etidronate-treated patients, no difference was found between the two arms. Similarly, there were no differences between the two arms with respect to the other outcome measures (new fractures, hypercalcemic episodes, and bone pain).

**Clodronate**—Three large randomized trials using oral clodronate in myeloma patients have been published. In a Finnish trial,[11] 350 newly diagnosed, previously untreated patients were entered, 336 of whom were randomized to receive either clodronate (2.4 g) or placebo daily for 2 years. All patients also received intermittent oral melphalan and prednisolone.

Only 204 (61%) patients had had radiographs at both study entry and after 2 years. Given this
limitation, the proportion of patients with progression of lytic lesions was lower in the clodronate-treated group than in the placebo group (12% vs 24%; P = .026). However, the two groups did not differ with regard to the progression of overall pathologic fractures, as well as both vertebral and nonvertebral fractures. In addition, the number of patients who developed hypercalcemia was comparable in the two arms. Changes in pain index and use of analgesics were similar in both arms.

Clodronate has also been evaluated in an open-label randomized German trial.[12] In this study, 170 previously untreated patients were randomized to receive either no bisphosphonate or oral clodronate (1.6 g/d) for 1 year. All of the patients were also treated with intravenous melphalan on day 1 and oral prednisone on days 1 through 4 every 4 weeks. Unfortunately, 52% of the participants prematurely terminated treatment despite the short length of the study (1 year).

Patients in the two arms showed no difference in the progression of bone disease, as assessed by plain radiographs. However, there was a trend toward a reduced number of new progressive sites in the clodronate-treated group after 6 months (P = .06), as well as 12 months (P = .09). The proportion of patients who were pain-free and who were not using analgesics was higher in the clodronate group. Because of the open design of this trial, one should be cautious in interpreting the results relative to analgesic usage and pain evaluation. No difference in performance status was observed.

Recently, the Medical Research Council (MRC) published the results of a large trial that randomized 536 patients with recently diagnosed myeloma to receive either oral clodronate (1.6 g) or placebo daily in addition to alkylator-based chemotherapy.[13] The primary end points of the trial were unclear. However, after combining the proportion of patients who developed either nonvertebral fractures or severe hypercalcemia (including those who left the trial due to severe hypercalcemia), the investigators found a lower incidence of these combined events in the clodronate-treated patients than in the placebo-treated patients (P = .021). Nevertheless, the overall number of patients who developed hypercalcemia was similar in the two arms.

In addition, the number of patients who experienced nonvertebral fractures was lower in the clodronate group (P = .036). Although vertebral fractures reportedly occurred significantly less frequently in clodronate-treated patients than in placebo recipients, only half of patients underwent even one post-baseline radiograph.

Back pain and poor performance status did not differ significantly between the two groups except at one time point (24 months). The proportion of patients requiring radiotherapy was similar in the two groups. There also were no differences between the groups in time to first skeletal event or overall survival.

It is somewhat surprising that this trial showed any benefit, given the negative results of the Finnish trial, which used a higher daily dose (2.4 g) of oral clodronate. The results of the MRC trial are limited by the lack of clearly defined, predetermined, specific primary and secondary end points. The lack of impact of this drug on time to first skeletal event and use of radiotherapy is also problematic.

**Pamidronate**--Compared with etidronate and clodronate, pamidronate is 100- and 10-fold more potent, respectively, in preventing bone resorption in vitro. This agent is a potent inhibitor of bone resorption at doses that do not affect bone mineralization.[14] In multiple myeloma patients, results of open-label trials lasting up to 24 months suggested that pamidronate disodium might be effective in reducing skeletal complications of multiple myeloma.

Based on these results, a randomized, double-blind study was conducted to determine whether monthly 90-mg infusions of pamidronate would reduce skeletal events in patients with multiple myeloma who were receiving chemotherapy, as compared with placebo.[10,15] This study included 392 patients with Durie-Salmon stage III multiple myeloma and at least one osteolytic lesion. Unlike the etidronate and clodronate trials, which involved untreated patients, patients in the pamidronate trial were required to receive an unchanged chemotherapy regimen for at least 2 months before enrollment.
Patients were stratified according to the type of antimyeloma therapy they were receiving at trial entry: first-line chemotherapy (stratum 1) or second-line or higher chemotherapy (stratum 2). Within each stratum, patients were randomized to receive either pamidronate disodium (90 mg) or placebo, each administered as a 4-hour intravenous infusion at intervals of 4 weeks for 21 months.

Because of the expected loss of patients on the trial, it was preplanned to analyze the primary efficacy variable (skeletal events) after 9 cycles of treatment and to analyze survival and safety after 21 cycles. However, patients continued to be followed for skeletal events during the entire 21 cycles of randomized treatment. Both the primary end point, skeletal events (pathologic fractures, spinal cord compression associated with vertebral compression fracture, surgery to treat or prevent pathologic fracture or spinal cord compression associated with vertebral compression fracture, or radiation to bone), and secondary end points (hypercalcemia, bone pain, analgesic drug use, performance status, and quality of life) were assessed monthly.

A total of 392 patients were enrolled in the study (205 patients received pamidronate and 187 patients received placebo), although efficacy was based on 377 patients. However, all 392 patients were included in the safety assessments and survival analyses. The chemotherapeutic regimens in the two groups were similar at study entry and during the trial.

After nine cycles of therapy, the proportion of patients having any skeletal event was 41% in the placebo group but only 24% in the pamidronate group (P < .001). In addition, median skeletal morbidity (defined as the number of skeletal events per year) was half as high in pamidronate-treated patients as in placebo recipients (P < .001). During the first nine treatment cycles, the proportion of pamidronate-treated patients with skeletal events was lower in both stratum 1 (first-line therapy) and stratum 2 (second-line or higher therapy).

During these first nine cycles, patients who received pamidronate had significant decreases in bone pain and required no increase in analgesic usage. The pamidronate-treated patients also showed no deterioration in performance status or quality of life at the end of 9 months.

Similar to the results after 9 cycles of therapy, the proportion of patients developing any skeletal event and skeletal morbidity continued to remain significantly lower in the pamidronate group than in the placebo group during the additional 12 randomized treatment cycles. However, the two treatment groups did not differ with respect to the percentage of patients with healing or progression of osteolytic lesions.

Overall survival in all 392 patients was not significantly different between the two treatment groups. Although median survival did not differ between the treatment groups in stratum 1 patients, median survival time was 21 months for stratum 1 patients treated with pam-idronate vs 14 months for their counterparts treated with placebo (Figure 2).

In a double-blind, randomized trial, a Danish-Swedish cooperative group compared oral pamidronate (300 mg/d) to placebo in 300 newly diagnosed myeloma patients who were also receiving intermittent melphalan and prednisone.[16] After a median duration of 18 months, there were no significant differences between the two arms with respect to either the primary end point, skeletal-related morbidity (defined as bone fracture, surgery for impending fracture, vertebral collapse, or increase in the number and/or size of lytic lesions) or secondary end points (hypercalcemic episodes or survival). Fewer episodes of severe pain and less height loss were observed in the pamidronate-treated patients, however.

Treatment Recommendations--Results of these trials show that the adjunctive use of bisphosphonates in addition to chemotherapy is superior to chemotherapy alone in patients with stage III multiple myeloma with respect to lessening bone complications. Bisphosphonate treatment should now be considered for all patients with multiple myeloma and at least one osteolytic lesion.

The three large long-term studies of clodronate show little impact of the oral form of this drug on skeletal complications. In addition, the lack of efficacy of oral pamidronate suggests that this route of administration is unlikely to produce positive results in multiple myeloma patients. Thus, the current drug of choice at present in the United States is intravenous pamidronate. Although 90 mg monthly
is efficacious, the optimal duration and dose of intravenous pamidronate are unknown. However, based on published results, patients should receive at least 21 months of treatment.[15]

Whether intravenous pamidronate is effective in earlier-stage disease or in patients without bone disease is unknown. However, recent in vitro studies suggest that pamidronate may possess antmyeloma properties, as demonstrated by its ability to induce apoptosis of myeloma cells[17] and suppress the production of interleukin-6, an important myeloma growth factor, by bone marrow stromal cells from myeloma patients.[18]

Breast Cancer

Metastasis of cancer to the skeleton occurs in 75% of patients with advanced breast carcinoma. On x-ray, the disease can be lytic, blastic, or, as is often the case, a combination of these processes. Breast cancer patients who have only skeletal disease can survive for a long period (20% alive at 5 years) with considerable morbidity and discomfort from their cancer-mediated bone destruction.

Clodronate--Two small studies reported that oral clodronate treatment could improve symptoms in patients with metastatic breast cancer.[19,20] These observations were confirmed by Paterson et al.[21] in a larger, randomized, double-blind, placebo-controlled study of oral clodronate, 1.6 g/d, in 173 patients. In patients who received clodronate, there was a significant reduction in episodes of hypercalcemia of malignancy, vertebral fractures, and the rate of vertebral deformity. No significant differences in nonvertebral fractures, radiation therapy for bone pain, or survival were observed. The combined rate of all skeletal events was significantly reduced in the pamidronate-treated patients, from 3.05 to 2.19 per year—a 33% reduction (P < .001). However, no difference was observed between the treatment groups with respect to time to first skeletal event.

Pamidronate--Several open-label studies by different European investigators suggested improvements in symptoms and on x-rays with a variety of doses and treatment schedules of pamidronate (usually 30 to 45 mg every 1 to 3 weeks).[23-25] Subsequently, a randomized, non-placebo-controlled study showed that oral pamidronate decreased the total number of skeletal complications.[26,27]

A dose-seeking study found that an 90-mg dose of intravenous pamidronate administered every 4 weeks was more effective than lower doses in reducing pain caused by bone metastases from breast cancer.[28] Two large, prospective, placebo-controlled, randomized clinical trials of intravenous pamidronate in breast carcinoma patients with lytic bone metastases have now been completed.[29-31] The first study enrolled 380 patients with stage IV breast carcinoma who were receiving cytotoxic chemotherapy, and the second enrolled 371 patients who were receiving endocrine therapy. All of the patients in both studies had at least one untreated lytic bone lesion measuring at least 1 cm in diameter.

In each study, patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 or 2-3 and were randomized, in double-blind fashion, to receive either pamidronate (90 mg) or placebo as a 2-hour intravenous infusion every 4 weeks for 2 years. In both studies, the two treatment groups were similar in demographic and prognostic factor profile.

The Breslow-Day test was performed to determine the homogeneity of results between the two studies. The test showed that the odds ratio of having a skeletal-related event (except hypercalcemia of malignancy) while receiving placebo as compared with pamidronate in the endocrine study did not differ significantly from the odds ratio in the chemotherapy study (P = .194). This justified the pooling of data from the two studies.

In a combined analysis of 751 patients with osteolytic bone metastases, the proportion of patients having any skeletal-related event, except hypercalcemia of malignancy (Figure 3), radiation administered to bone, and any pathologic fractures by the end of 24 months of therapy was significantly lower in those receiving pamidronate than in those given placebo. Pamidronate-treated patients also had significantly lower skeletal morbidity (number of events per year), received fewer courses of radiation to bone, and suffered fewer pathologic fractures per year. The time to first
skeletal-related event was significantly increased in the pamidronate group, from 7.0 to 12.7 months, and the time to first fracture was increased from 12.8 to 25.2 months.

In each study, bone pain and use of narcotics increased to a lesser extent and performance status deteriorated more slowly in the pamidronate-treated patients than in the placebo group. Unfortunately, neither study showed a survival difference between the two groups.

**Other Cancers That Metastasize to Bone**

Skeletal metastases from prostate cancer are usually osteoblastic. Histomorphometric and biochemical studies have also shown an increase in bone resorption in patients with metastatic prostate cancer. An analgesic effect of bisphosphonates seems to parallel the inhibition of bone resorption in these patients. However, no large-scale, double-blind trials have been completed to guide the use of bisphosphonates in metastatic prostate cancer. Large phase III studies have been initiated recently.

No large studies have been published evaluating the use of bisphosphonates in patients with osteolytic bone metastases from other cancers, although several such trials are currently in progress. These include studies in all cancers with lytic bone metastases.

**Prevention of Bone Metastases**

The ultimate goal of antiosteoclastic therapy should be the prevention of bone metastases. Both attachment of breast and prostate cancer cells to bone mineral is decreased in the presence of bisphosphonates.[32,33] Moreover, development of bone metastases in nude mice infused with a human breast cancer cell line is inhibited by bisphosphonates.[34]

Several clinical studies have suggested that bisphosphonate therapy can retard the formation of new bone metastases in patients with metastatic bone disease; these include recent studies involving the use of monthly 45-mg doses of intravenous pamidronate.[35] Two studies using oral clodronate did not demonstrate this effect.[36,37] However, a study presented at the 1997 American Society of Clinical Oncology meeting and recently published in *The New England Journal of Medicine* suggested that oral clodronate (1.6 g/d) may reduce the development of both osseous and nonosseous metastases in high-risk breast cancer patients.[38]

**Future Prospects**

Third-generation bisphosphonates (eg, zoledronate and ibandronate) that appear to be more than 100 times more potent than second-generation aminobisphosphonates have recently entered clinical trials. Very small doses of these agents effectively restored normocalcemia in patients with tumor-induced hypercalcemia.[39] These newer drugs not only may provide palliative effects in patients with tumors that have a predilection for bone but also may be able to prevent the devastating problem of the spread of cancer to bone. Moreover, they may improve the overall survival of these patients while maintaining their quality of life.

**Conclusions**

Metastatic bone disease is often associated with significant morbidity and a poor quality of life. Large, randomized clinical trials in patients with myeloma and breast cancer who have metastatic bone disease have shown that monthly administration of intravenous pamidronate as a supplement to antitumor therapy reduces the morbidity associated with bone metastasis. Infusion of this agent decreases the development of all skeletal complications, particularly, new pathologic fractures, and also reduces the need for radiotherapy to bone. Moreover, pamidronate-treated patients experience less bone pain, require fewer analgesics, and have a slower deterioration in their quality of life.

These studies have demonstrated continued benefit for the duration of the trials (approximately 2 years). Whether similar efficacy will be shown in other cancers metastatic to bone is the subject of
several current clinical studies.

On the other hand, the use of daily oral pamidronate and other oral bisphosphonates has achieved limited clinical benefit. Although some studies suggest a modest reduction in fractures and specific hypercalcemic episodes, the time to first skeletal complication and requirement for radiotherapy have not been significantly influenced by oral bisphosphonates. The poor, erratic absorption of orally administered bisphosphonates, as well as the drugs' gastrointestinal side effects, may explain their lack of efficacy in these patients.

Recent clinical and laboratory studies suggest that bisphosphonates may also influence tumor cells themselves in a number of ways. These agents have been shown to inhibit attachment of cancer cells to bone and reduce the development of bone metastases. In addition, bisphosphonates decrease production of cytokines that promote tumor growth and induce apoptosis of tumor cells.

In support of this, use of intravenous pamidronate prolonged survival in myeloma patients receiving salvage chemotherapy. The new, more potent, third-generation bisphosphonates hold promise for improving the survival as well as the quality of life of patients with metastatic bone disease.

References:


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