

The Role of Bisphosphonates in Multiple Myeloma

Multiple myeloma is characterized by bone destruction that often leads to some of the most debilitating manifestations of this disease: pain, hypercalcemia, osteopenia, pathologic fractures, and spinal cord compression. These clinical manifestations are due not only to myeloma deposits in the bone, which lead to focal bone destruction, but also to increased osteoporotic activity, resulting in bone resorption. Chemotherapy, even when successful, does not produce skeletal healing, and the dual risks of osteopenia and pathologic fracture persist. Fortunately, this often grim situation has at last begun to yield to pharmacologic intervention since the administration of bisphosphonates has been found to reduce the bone destruction caused by multiple myeloma.

Chemically, the bisphosphonates consist of a phosphorus-carbon-phosphorus backbone and two additional chains (R_1 and R_2) of variable structure (Figure). This structure confers some highly desirable characteristics on these compounds. For instance, the substitution of a carbon atom for oxygen makes the pyrophosphates resistant to hydrolysis and preserves their inhibition of bone resorption. In addition, if the R_1 position is occupied by a hydroxyl group, the molecule has a high affinity for calcium crystals and bone mineral, accounting for its binding to hydroxyapatite crystals in the mineralized bone matrix (1). This results in interference with osteoclastic activity, probably by preventing the attachment of osteoclast precursors to bone. Different chemical groups at the R_2 site account for variability in antiresorptive potency (2).

In general, bisphosphonates are poorly absorbed

when administered orally. In addition, many foods, beverages, and medications can reduce drug absorption. Significant gastrointestinal toxicity, manifested by esophagitis, is an additional potential problem with oral administration (3).

Etidronate, a weak bisphosphonate, has not been found to be beneficial in the treatment of myeloma bone disease (4). However, clodronate, which is 10 times more potent than etidronate, was reported to decrease bone pain and pathologic fractures in osteoclastic lesions in a placebo-controlled study of 68 patients with multiple myeloma (5). In a Finnish study of 336 patients with newly diagnosed multiple myeloma who received melphalan and prednisone, participants were randomly assigned to receive clodronate (2.4 g/d) or placebo for 2 years. Lytic lesions progressed in 12% of the clodronate group and in 24% of the placebo group ($P = 0.026$). However, no differences were found between the two

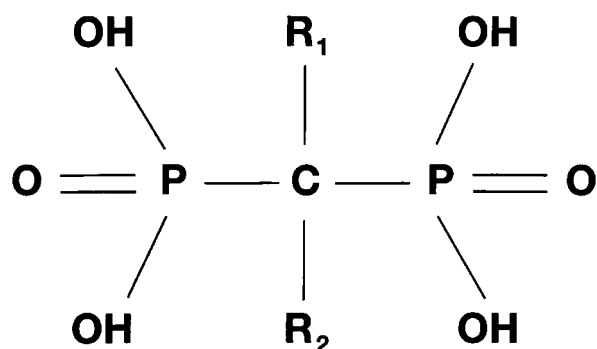


Figure. Backbone chemical structure of a bisphosphonate. Reprinted from Coukell and Markham (1) with permission from *Annual Reviews*.

groups for analgesic use, pathologic compression fractures, or incidence of hypercalcemia (6). In a Medical Research Council study, 536 patients with newly diagnosed multiple myeloma were randomly assigned to receive oral clodronate, 1.6 g/d, or placebo. Patients who received clodronate had fewer vertebral fractures, less height loss, and a 50% decrease in severe hypercalcemia, as well as fewer nonvertebral fractures. The investigators reported that clodronate-treated patients without overt skeletal disease at the time of diagnosis developed 40% fewer fractures and had less height loss than those receiving placebo (7).

Pamidronate, a second-generation bisphosphonate, is 100-fold more potent in bioassay than etidronate and has a plasma half-life of less than 1 hour (1). It is the bisphosphonate most commonly used in patients with multiple myeloma. The bisphosphonates are eliminated almost exclusively by renal excretion. Although renal insufficiency results in delayed excretion, pamidronate does not seem to cause nephrotoxicity (8). It can be administered both orally and intravenously. When the intravenous route is chosen, approximately half of the administered dose reaches bone and is concentrated at the surface, where bone remodeling takes place. In general, however, bisphosphonates bind more avidly to trabecular bone than to cortical bone. Pamidronate is a potent inhibitor of bone resorption but does not affect bone mineralization.

In a prospective study of 392 patients with stage III multiple myeloma who had more than one lytic lesion, patients were randomly assigned to receive either pamidronate (90 mg) or placebo by 4-hour intravenous infusion every 4 weeks. All patients received antimyeloma therapy that had been unchanged for the previous 2 months. At 9 months, a skeletal event (defined as pathologic fracture, spinal cord compression, need for bone radiation, or orthopedic skeletal procedures) had occurred in 41% of the placebo group and 24% of the pamidronate group ($P \leq 0.001$). The skeletal morbidity rate (defined as the number of skeletal events divided by the duration of therapy in years) was 2.05 for the placebo group and 1.1 for the pamidronate group ($P \leq 0.001$). The median time to the first skeletal event was 10 months in the placebo group and was not reached in the pamidronate group. In addition, pain scores and the need for analgesics were lower in the pamidronate group, whereas quality of life (measured by the Eastern Cooperative Oncology Group and Spitzer criteria) was superior. No differences in the healing or progression of osteoclastic lesions were seen on radiography. Pamidronate was well tolerated; few patients had skeletal pain, hypocalcemia, or fever, and these problems were easily managed (9). The benefits of pamidronate contin-

ued throughout the study, which was extended for a total of 21 months. Despite these benefits, overall survival did not differ between patients who received pamidronate and those who received placebo (26 and 24 months; $P = 0.377$), although if only patients receiving a second or subsequent course of antimyeloma therapy were considered, those who received pamidronate lived longer (21 and 14 months; $P = 0.04$) (10).

In contrast to the favorable results obtained from intravenous administration of bisphosphonates in patients with myeloma, oral administration has been relatively unsuccessful. In a recent study, 300 patients with multiple myeloma being treated with melphalan and prednisone were randomly assigned to receive oral pamidronate, 3 mg/d, or placebo. At a median of 550 days of treatment, no statistically significant reduction in skeletal fractures, disease-related orthopedic surgery, vertebral collapse, or the number or size of lytic lesions was demonstrated, nor was the frequency of hypercalcemia or survival affected. However, the pamidronate group experienced fewer cases of severe pain and less reduction in height. The investigators attributed the relative lack of response to poor resorption of pamidronate by the oral route (11). Ten patients from the study who received oral pamidronate and six who received placebo were studied by using histomorphometry, analysis of cytokines, and biochemical markers of bone turnover. The pamidronate-treated patients were noted to have a reduction in overall bone resorption rate and bone turnover without impairment of osteoclastic bone formation (12).

Third-generation bisphosphonates include zoledronate and ibandronate. Zoledronate is 100 to 850 times more potent than pamidronate, depending on the assay used. It must be given intravenously, but the infusion time can be reduced to only a few minutes. Studies comparing zoledronate and pamidronate are currently under way. In one study, 198 patients with multiple myeloma were randomly assigned to receive intravenous ibandronate or placebo. Although no difference in skeletal-related events was noted, bone resorption markers were reduced in the ibandronate group (13). It was thought that the dosage of ibandronate was too low to produce clinically useful results.

One of the more intriguing outcomes of this work with bisphosphonates in myeloma is that in addition to their effects on bone turnover, these drugs appear to have an antitumor effect. Shipman and colleagues (14) reported that bisphosphonates can induce apoptosis in human myeloma cell lines. They demonstrated that bisphosphonate-induced apoptosis in human myeloma cells is the result of inhibition of the mevalonate pathway (15). Pamidronate has also been reported to inhibit growth of

myeloma in vivo in the severe combined immunodeficiency–human myeloma cell system (16, 17) and to reduce bone marrow plasma cells in multiple myeloma (18). Zoledronate-induced cytotoxicity is greater than that produced by pamidronate.

Considering what we now know of this class of drugs, intravenous administration of bisphosphonates can be recommended for treatment of multiple myeloma patients with one or more lytic lesions or when severe osteoporosis is detected by skeletal radiography. The appropriate timing of bisphosphonate therapy has not yet been thoroughly investigated, but it seems reasonable at this point to initiate use of the drug when chemotherapy is started and to continue treatment indefinitely. Bisphosphonate treatment should not be terminated even if the patient sustains a fracture or other skeletal event. Oral administration of currently available bisphosphonates cannot be recommended because of their lack of effectiveness. The third-generation bisphosphonates zoledronate and ibandronate may eventually become the agents of choice because they can be administered intravenously in a matter of minutes rather than the 2 to 4 hours required for pamidronate administration.

Multiple myeloma is a difficult and frustrating disease to treat, and although bisphosphonates are clearly not a panacea, they represent an advance in skeletal benefit and symptom control that is meaningful for both patients and physicians. We do not yet know whether the suggestive antitumor properties of bisphosphonates will be helpful. Lovastatin and simvastatin increase the expression of bone morphogenetic protein-2 gene in mice, resulting in increased bone formation (19). Possibilities such as these must be confirmed with careful scientific observation. Although we cannot expect that every hypothesis will bear fruit, we can expect that advances in one discipline may lead to surprising advances in unrelated areas, and we know that good observation often leads to unexpected rewards.

Robert A. Kyle, MD
Mayo Clinic and Mayo Foundation
Rochester, MN 55905

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Requests for Single Reprints: Robert A. Kyle, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

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