Introduction: the evolving role of bisphosphonate therapy in multiple myeloma

Noopur Raje and Kenneth C. Anderson

Bone disease is a hallmark of multiple myeloma (MM) and contributes to most of the debilitating morbidity associated with this disease. Bone lesions result not only from the direct deposits of MM cells within the bone, but also from the release of soluble factors by both the tumor and the microenvironment, resulting in the stimulation of osteoclast activity and bone resorption. The use of pharmacologic intervention with bisphosphonate therapy has resulted in a significant reduction in skeletally related events such as the occurrence of pathologic fractures, lytic lesions, bone pain, and hypercalcemia. In addition, their use has recently been shown to provide a survival benefit in a subset of MM patients. In this issue of Blood, Kunzmann et al reveal a novel antitumor effect of aminobisphosphonates through their stimulation of γδT cells and the induction of an anti–MM activity in patient samples. Their study is a seminal finding and possibly reflects an alternative mechanism by which these drugs might play an immunomodulatory role in MM.

Bisphosphonates contain 2 phosphonate groups attached to a single carbon atom, forming a “P-C-P” structure, and represent stable analogues of naturally occurring pyrophosphate-containing compounds. Bisphosphonates adsorb to bone mineral and inhibit bone resorption. On the basis of the presence of a hydroxyl group, these molecules display a high binding affinity for hydroxyapatite crystals in mineralized bone matrix, resulting in interference with osteoclastic activity and an inhibition of bone resorption. In addition to inhibition of osteoclasts, the ability of bisphosphonates to reduce the activation frequency and birth rates of new bone remodeling units, and possibly to enhance osteon mineralization, may also contribute to the reduction in pathologic fractures in patients with osteopenia. Recent studies show that bisphosphonates can be classified into at least 2 groups with different modes of action. Bisphosphonates that closely resemble pyrophosphates (such as clodronate and etidronate) can be metabolically incorporated into nonhydrolyzable analogues of adenosine triphosphate (ATP) that may inhibit ATP-dependent intracellular enzymes. The more potent nitrogen-containing bisphosphonates (such as pamidronate, alendronate, risedronate, and ibandronate) are not metabolized in this way but can inhibit enzymes of the mevalonate pathway, thereby preventing the biosynthesis of isoprenoid compounds that are essential for the posttranslational modification of small guanidine triphosphateses (GTPases). The inhibition of protein prenylation and the disruption of the function of these key regulatory proteins explain the loss of osteoclast activity and induction of apoptosis. It is of interest to note that Mundy et al have shown stimulation of new bone formation by statins, a group of commonly used cholesterol-lowering drugs (hydroxymethylcoenzyme A reductase inhibitors) acting further upstream in the mevalonic acid pathway, which is also a target of bisphosphonates.

MM is a clonal B-cell neoplasm that affects terminally differentiated B cells, ie, plasma cells. In the year 2000, MM will be diagnosed in approximately 13 700 people in the United States and will account for 20% of deaths from hematologic malignancies. Despite the use of aggressive approaches including myeloablative therapy, this disease remains fatal. These are, however, exciting times in myeloma research. Novel therapeutic interventions such as posttransplant immunotherapy approaches and the use of pharmacologic interventions including drugs such as thalidomide offer great promise. Kunzmann et al report an interesting effect of bisphosphonates on T cells resulting in indirect effects on MM cells. To date, the role of bisphosphonates has been as supportive therapy for MM bone disease. Although a weak bisphosphonate, etidronate, was not found to be effective in MM bone disease, clodronate, which is 10 times more potent, demonstrated a significant decrease in the development of osteolytic lesions and other skeletally related complications in 2 placebo controlled randomized trials. Pamidronate, a second-generation bisphosphate, is 100-fold more potent than etidronate and can be given intravenously. In a prospective randomized trial, patients with stage III MM and at least 1 lytic lesion were treated with either placebo or pamidronate (90 mg) as a 4-hour intravenous infusion given every 4 weeks for 9 cycles as a supplement to antimonyeloma therapy. Among 392 patients enrolled, the efficacy of treatment could be evaluated in 196 patients who received pamidronate and 181 patients who received placebo. The proportion of patients who had any skeletal events was significantly lower in the pamidronate group (24%) than in the placebo group (41%, P < .001). Patients who received pamidronate also had significant decreases in bone pain and maintained both performance status and quality of life. Subsequently, this study was extended to 21 cycles of pamidronate therapy. After 21 cycles, the proportion of patients who developed any skeletal event remained lower in the pamidronate group (P = .015). The mean number of skeletal events per year also remained lower in the pamidronate group (1.3) than in placebo-treated patients (2.2; P = .008). Although overall survival did not differ between the pamidronate-treated group and placebo patients, those patients receiving a second or subsequent course of chemotherapy who were randomized to also receive pamidronate lived longer than patients on salvage therapy who did not receive pamidronate (14 vs 21 months, P = .041). Third-generation bisphosphonates include zoledronate and ibandronate. Zoledronate is 100 to 850 times more potent than pamidronate, and studies are underway comparing pamidronate with zoledronate.

The antiresorptive effect of bisphosphonates and their molecular effects on osteoclasts and osteoblasts are now being defined. Even more intriguing, however, are the insights into their novel mechanisms of actions, such as stimulating T-cell proliferation and
function, as elegantly demonstrated by Kunzmann et al. Recent evidence suggests that certain bisphosphonates may exert a direct antitumor effect by inducing apoptosis and cell-cycle arrest in human MM cells in vitro. It has been previously demonstrated that certain low-potency antiresorptive bisphosphonates such as clodronate can be metabolized to potentially cytotoxic analogues of ATP, whereas the more potent nitrogen-containing bisphosphonates, including alendronate, imidronate, and ibandronate, do not appear to be metabolized. These latter drugs inhibit enzymes of the mevalonate pathway and induce apoptosis of MM cells by preventing protein isoprenylation. A caveat about these studies, however, is that in most cases the drug concentrations used are more than 10 μmol/L, which is much higher than the peak serum concentrations achieved by patients on bisphosphonate therapy and suggests a potential nonspecific cytotoxic effect of these drugs. In contrast, the doses of bisphosphonates inducing osteoclast apoptosis occurs at clinically relevant drug concentrations. When used at doses of 4 μg/d per mouse, ibandronate reduced osteolytic lesions in a murine myeloma bone disease model, without having a direct effect on MM cells. Anecdotal data also support an in vivo antitumor effect of pamidronate.

There is also evolving evidence that bisphosphonates may act by inhibiting cytokines. The role of bone marrow stroma and adhesion molecule profile in the propagation and potentiation of MM has been demonstrated in multiple studies. Additionally, interleukin (IL)–6 has been shown to be an important growth and survival factor for MM. Although controversy surrounds the exact source of IL-6 in MM pathogenesis, there is evidence to suggest both an autocrine and a paracrine production of IL-6. IL-6–mediated paracrine MM cell growth is supported by observations that bone marrow stromal cells (BMSCs) are the major source of IL-6 in MM, that freshly isolated MM cells cultured without IL-6 in MM, that freshly isolated MM cells cultured without bone marrow stromal cells (BMSCs) are the major source of IL-6 in MM, that freshly isolated MM cells cultured without exogenous IL-6 rapidly stop proliferating, and that adhesion of MM cells to BMSCs up-regulates IL-6 secretion by BMSCs. In addition, adhesion of osteoblasts to MM cells appears sufficient to trigger IL-6 transcription and secretion by the BMSCs. Other osteoclast-activating factors (OAFs), such as IL-1β and tumor necrosis factor (TNF)–β are also secreted. These OAFs prompt the BMSCs and the osteoblasts to secrete TRANCE, a new member of the TNF family. Tumor necrosis factor–related activation–induced cytokine (TRANCE) in turn induces differentiation and maturation of osteoclast progenitors, resulting in increased osteoclastic activity and release of certain cytokines such as IL-6, basic fibroblast growth factor, and transforming growth factor β, all of which contribute to tumor cell growth and survival. Recent evidence suggests that pamidronate and zoledronate inhibit the production of IL-6 by BMSCs at concentrations of 1 μmol/L or less. In addition to the role of tumor/stroma interaction in the growth and survival of myeloma, recent evidence suggests that activation of very-late-antigen–4 in the extracellular matrix confers drug resistance as measured by cytotoxicity and apoptosis assays. Preliminary data suggest that bisphosphonates might modulate adhesion molecule profile and thereby overcome drug resistance. Finally, matrix metalloproteinases (MMPs) are also known to play a critical role in bone remodeling and tumor invasion. MMP-1 secretion was also inhibited by the addition of bisphosphonates; in contrast, MMP-2, which has been implicated in the metastatic process, was increased by these bisphosphonates.

MM has long been a target for immunologic interventions. In the autologous setting, vaccination strategies with dendritic cells pulsed with MM antigens, MM cell–dendritic cell fusions, carrier-linked idiotype protein, and catalytic subunit of telomerase or DNA encoding for single-chain variable fragments linked to a carrier protein gene are under investigation. Whole-tumor vaccination strategies are also being examined and include the use of MM cells transfected and/or stimulated with cytokines, costimulatory molecules, or CD40 ligand. Strategies to induce allogeneic anti-MM immunity have included immunization of the marrow donor to idiotypic protein, as well as donor lymphocyte infusions. Of great interest are the possible immunomodulatory effects of drugs such as thalidomide, its immunomodulatory derivatives, and the bisphosphonates. Besides having a direct effect on tumor cells, thalidomide and its analogues result in an expansion of T cells toward a Th1 response, resulting in interferon γ and IL-2 production. The new effects of the bisphosphonates demonstrated by Kunzmann et al. occurred the expansion of γδT cells, and the enhancement of MM-specific cytotoxicity add a new dimension to our armamentarium against MM. The effects of bisphosphonates on γδT cells reported by Kunzmann et al occurred at doses that are pharmacologically achievable and therefore of enormous interest.

An understanding of cellular and molecular mechanisms regulating myeloma cell growth and survival will derive novel therapies to specifically inhibit tumor cell growth and/or trigger apoptosis and simultaneously target the bone marrow microenvironment. The discovery that bisphosphonates may directly induce apoptosis of MM cells, as well as indirectly effect BMSCs and T-cell function, both supports their use as supportive therapy and further suggests their potential utility as primary therapy for MM.

References

14. Shipman CM, Croucher PI, Russell RG, Helfrich MH, Rogers MJ. The bisphosphonate...