

Pathophysiology of Bone Metastases: How This Knowledge May Lead to Therapeutic Intervention

Allan Lipton, MD

The development of bone metastasis is common in many cancers, occurring in virtually all patients with multiple myeloma, in 65%–75% of patients with advanced breast and prostate cancers, and in 30%–40% of patients with lung cancer (Table 1) [1–3]. Bone lesions put these patients at high risk of skeletal complications, including pathologic fracture, spinal cord compression, surgery to bone, debilitating bone pain, and hypercalcemia. Because of the high incidence of bone metastases in patients with solid tumors and the relatively long survival time after diagnosis of bone metastasis, therapies to reduce morbidity from skeletal complications in these patients are important [1–3].

Bone metastasis is common in cancer patients, most likely because of the favorable microenvironment of the bone matrix and its ample blood supply. Metastasis of tumor cells to bone requires a complex cascade of events involving detachment from the primary tumor site, invasion of the vasculature, migration and adherence to distant capillaries of the bone, extravasation, and proliferation [4]. Once tumor cells have invaded the bone matrix, they produce growth factors that can directly or indirectly stimulate osteoclasts to degrade the bone. As a result, growth factors that can stimulate tumor cell growth are released from bone, thus establishing a vicious cycle of bone destruction and local tumor growth.

Bone lesions are classified as osteolytic or osteoblastic, based on their radiographic appearance [4]. Osteolytic lesions are the result of increased osteoclast activity accompanied by a concomitant decrease in osteoblastic activity, leading to an abnormally high rate of bone resorption. Osteoblastic lesions are characterized by increased bone forma-

Abstract Bone metastases are common in many advanced cancers and are a clinically relevant source of skeletal morbidity. The bone mineral matrix contains numerous growth factors that are released during normal bone remodeling, providing a fertile microenvironment for tumor cell colonization and proliferation. Tumor cells then release a variety of growth factors that promote bone resorption and increase the risk of skeletal complications. Bisphosphonates are potent inhibitors of osteoclast activity that have demonstrated efficacy in the treatment of bone metastases. Bisphosphonates bind avidly to the bone matrix, are released during bone resorption, and are subsequently internalized by osteoclasts, where they interfere with biochemical pathways and induce osteoclast apoptosis. Bisphosphonates also antagonize osteoclastogenesis and promote the differentiation of osteoblasts. As a result, bisphosphonates inhibit tumor-induced osteolysis and reduce skeletal morbidity. Furthermore, preclinical studies suggest that bisphosphonates possess antitumor activity and can inhibit proliferation and induce apoptosis of tumor cell lines. In addition, zoledronic acid, a new-generation bisphosphonate, appears to inhibit tumor cell invasion of the extracellular matrix. These data suggest that zoledronic acid and other bisphosphonates may play a role in the reduction of skeletal tumor burden and the prevention of bone metastasis.

tion around tumor cell deposits, but they are also combined with unbalanced osteolytic activity and marked increases in bone turnover, as evidenced by increased markers of bone resorption in the serum and urine of those patients [5]. Both types of bone lesions result in significant local bone loss and potential vertebral collapse. Typically, multiple myeloma is associated with osteolytic lesions, prostate cancer is associated with osteoblastic lesions, and breast cancer is associated with mixed lesions [3].

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and are effective in the treatment of a variety of bone diseases. They bind avidly to the bone mineral and accumulate in the bone mineral matrix at sites of active metabolism. Bone resorption releases bisphosphonates from the bone, and they are internalized by osteoclasts,

Dr. Lipton is Professor of Medicine, Division of Oncology, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pennsylvania.

Correspondence to: Allan Lipton, MD, Milton S. Hershey Medical Center, PO Box 850 H-46, Hershey, PA 17033; telephone: (717) 531-8677; fax: (717) 531-5076; e-mail: alipton@psu.edu

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Table 1**Metastatic Bone Disease Is Prevalent in Many Types of Cancer**

CANCER	FIVE-YEAR WORLD PREVALENCE ¹	INCIDENCE OF BONE METASTASES IN CANCERS ²	MEDIAN SURVIVAL (MONTHS) ^{2,3}
Myeloma	144,000	70%–95%	6–54
Renal	480,000	20%–25%	6
Melanoma	533,000	14%–45%	6
Thyroid	475,000	60%	48
Lung	1,394,000	30%–40%	6
Breast	3,860,000	65%–75%	19–25
Prostate	1,555,000	65%–75%	12–53

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thereby inhibiting their bone-resorbing activity and inducing osteoclast apoptosis [6]. Furthermore, bisphosphonates have been shown to inhibit osteoclastogenesis in vitro and in vivo [7, 8].

Preclinical studies suggest that bisphosphonates also possess antitumor activity through a variety of mechanisms, including inhibition of tumor growth, induction of apoptosis, and inhibition of tumor cell invasion of the extracellular matrix [9–11]. These studies, as well as in vivo data from animal models of prostate cancer and breast cancer, suggest that bisphosphonates may prevent tumor metastasis to bone and delay disease progression in the bone [12–14].

Bisphosphonates are commonly used to treat patients with bone metastases [2]. Zoledronic acid (Zometa), a new-generation bisphosphonate, is effective in the treatment of osteolytic, mixed, and osteoblastic bone lesions and is effective in reducing and delaying the onset of skeletal complications in patients with multiple myeloma, breast cancer, prostate cancer, and a variety of other solid tumors [15–18]. Further investigations into the biochemical mechanisms of the inhibition of bone resorption and antitumor activity of bisphosphonates could provide insight into additional therapeutic advantages.

Pathophysiology of Bone Metastases

Bone normally undergoes continual remodeling in response to mechanical stress via the dynamic and orchestrated interactions of osteoclasts and osteoblasts alternately resorbing and repairing bone, respectively, and the mineralized bone matrix contains numerous growth factors that are released during this process [19]. Bone remodeling begins with the activation of osteoclasts by local events, including the release of interleukin-1 (IL-1), leading to bone resorption and the release

of other growth factors. These factors, including transforming growth factor-beta (TGF- β) and insulin-like growth factor II (IGF-II), increase the proliferation and differentiation of osteoblasts, which subsequently form new bone at the site of resorption, thus maintaining bone integrity and strengthening the bone.

The skeleton is the most common site of metastasis in many advanced cancers, and metastasis of tumor cells to the bone matrix involves a complex cascade of events (Figure 1) [19]. Bone metastasis begins when primary tumor cells detach from their place of origin by forming new blood vessels and invading the vasculature. These tumor cells then form aggregates and eventually adhere to the vascular endothelial cells of distant capillaries of the bone. Subsequently, the cells escape the circulation, invade the marrow stroma, and eventually adhere to the endosteal surface of the bone (ie, at the interface of bone and marrow) and proliferate.

In addition to the numerous growth factors present in the mineralized bone matrix, the bone marrow consists of hematopoietic stem cells, stromal cells, and immune cells that release a number of cytokines and growth factors [19]. This fertile microenvironment promotes the growth of tumor cells that have migrated to bone. Once tumor cells have colonized in the bone matrix, they secrete a plethora of soluble growth factors that stimulate the activity of osteoclasts and/or osteoblasts and disrupt normal bone remodeling (Figure 2) [20]. The activation of osteoclasts and bone resorption causes further release of bone-derived growth factors that enhance survival and proliferation of the tumor cells. As a result, the normal homeostasis of the bone is disrupted and excess bone resorption ensues.

FACTORS IN THE METASTATIC PROCESS

Tumor cells from breast cancer and prostate cancer form metastatic colonies in the bone more readily than do tumor cells from other types of cancer, indicating that they express a phenotype that aids in the metastatic process. A variety of factors have been implicated in the metastatic process, including proteolytic enzymes, cell adhesion molecules (CAMs), and growth factors. Proteolytic enzymes are necessary for tumor cells to detach from their primary site, invade the surrounding soft tissue, enter and exit the vasculature, and degrade the bone matrix. Matrix metalloproteinases (MMPs) have been implicated in bone resorption and tumor progression [19]. In human myeloma

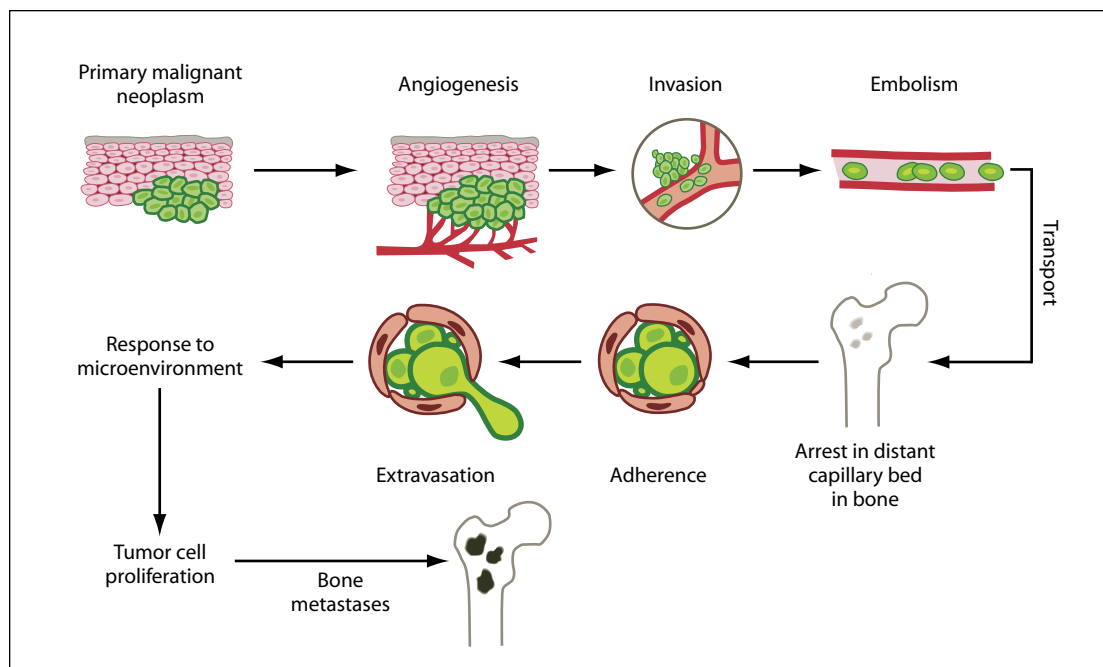


Figure 1 Mechanism of Tumor Metastasis to Bone

Multiple steps are involved in the metastasis of tumor cells from the primary tumor site to the skeleton. Adapted with permission from Guise and Mundy [19].

cells, MMP-9 is constitutively expressed, and coculture of these cells with bone marrow stromal cells increases MMP activity [21].

CAMs, such as integrins, play a critical role in tumor invasion, metastasis, and proliferation [22]. Loss of CAMs at the primary site facilitates the detachment of cancer cells from the primary tumor. Similarly, increased expression of CAMs at the site of metastasis may be necessary for cells to arrest and attach to the extracellular matrix. Integrins, the most abundant of CAMs, are involved in angiogenesis and are necessary for osteoclast-mediated bone resorption [19]. Studies have demonstrated that expression of integrin $\alpha_v\beta_3$ in tumor cells increases tumor cell invasion and the development of osteolytic lesions in nude mice [23]. Furthermore, antagonists of integrin $\alpha_v\beta_3$ inhibit bone resorption and tumor angiogenesis, and a recent study demonstrated that ablation of integrin $\alpha_v\beta_3$ expression in mice by a germline-targeted disruption of the β_3 integrin subunit resulted in inhibition of osteolytic bone metastases after inoculation with the B16 murine melanoma cell line [24].

OSTEOLYSIS: AN IMPORTANT FIRST STEP

Preclinical evidence strongly suggests that induction of osteolysis is an important first step in

the formation of bone metastases. For example, androgen-deficient mice have higher levels of bone resorption markers than control mice and develop more bone metastases when inoculated with hormone-resistant prostate cancer cell lines [13]. Tumor cells secrete parathyroid hormone-related protein (PTHrP) and IL-6, which are powerful mediators of osteoclast activation (Figure 2) [20]. PTHrP is expressed in human breast cancer cells in vivo, and higher levels of expression are associated with sites of bone metastases, compared with soft-tissue metastases or primary-tumor sites [25]. Mice inoculated with a human breast cancer cell line expressing high levels of PTHrP develop predominantly osteolytic bone metastases [26].

Interestingly, PTHrP has also been described in prostate cancer cells, in both primary tumors and bone metastases, indicating that bone metastases from prostate cancer also have an osteolytic component [27]. PTHrP, parathyroid hormone (PTH), IL-1, IL-6, and IL-11 participate in osteolysis by stimulating the production of receptor activator of nuclear factor- κ B ligand (RANKL) by osteoblasts and stromal cells [4]. RANKL binds to its receptor (RANK) on osteoclast progenitors, leading to the differentiation of the progenitors into mature

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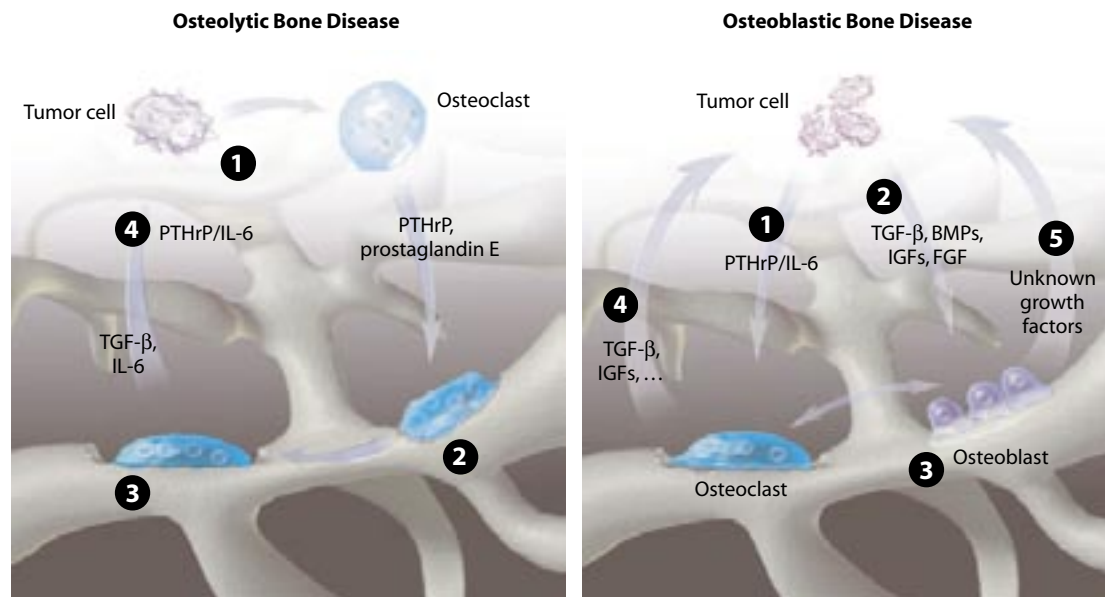


Figure 2 Pathophysiology of Bone Metastases

Left In osteolytic bone disease, (1) metastatic tumor cells release humoral factors that stimulate osteoclastic recruitment and differentiation. (2) Osteoclasts begin to break down bone. (3) Bone resorption results in the release of growth factors that stimulate tumor cell growth. (4) As the tumor proliferates, it produces substances that increase osteoclast-mediated bone resorption.

Right In osteoblastic bone disease, (1) metastatic tumor cells release growth factors that stimulate the activity of osteoclasts. (2) Tumor cells also secrete growth factors that stimulate the activity of osteoblasts. (3) Excessive new bone formation occurs around tumor-cell deposits. (4) Osteoclastic activity releases growth factors that stimulate tumor cell growth. (5) Osteoblastic activation releases unidentified osteoblastic growth factors that also stimulate tumor cell growth.

TGF- β = transforming growth factor-beta; IL-6 = interleukin-6; PTHrP = parathyroid hormone-related protein; BMP = bone morphogenetic protein; IGF = insulin-like growth factor; FGF = fibroblast growth factor. Adapted in part with permission from Saad and Schulman [20].

osteoclasts and initiation of bone resorption. Evidence for the involvement of RANKL in bone resorption is demonstrated by studies showing that osteoclastogenesis, bone degradation, and tumor growth in the bone are prevented by expression of osteoprotegerin (OPG), a protein that blocks the interaction of RANKL and RANK [28].

PATHOPHYSIOLOGY OF OSTEOLASTIC LESIONS

Osteoblastic lesions are the result of the production of soluble paracrine factors by the tumor cell that stimulate bone formation by increasing osteoblast activity (Figure 2) [20]. They include TGF- β , bone morphogenetic proteins (BMPs), and endothelin-1 [29]. Members of the TGF- β family, particularly isoforms 1 and 2, stimulate new bone formation in vivo and are expressed by human prostate cancer cell lines and prostate tumors [30, 31]. Bone morphogenetic proteins are members of the extended TGF- β superfamily

synthesized by bone cells and have been shown to stimulate osteoblast differentiation and induce new bone formation in vivo [32]. Furthermore, various BMPs are expressed in a number of rat and human prostate cancer cell lines and in normal and neoplastic human prostate tissue [33]. Endothelin-1 (a growth factor that stimulates osteoblasts in culture) is significantly elevated in the circulation of patients with prostate cancer and bone metastases and is secreted by many prostate cancer cell lines [34]. Furthermore, endothelin-1 is expressed and secreted by breast cancer cell lines that form osteoblastic lesions, and the incidence of metastases is decreased by treatment with an endothelin-A-receptor antagonist [35]. Additional factors secreted by cancer cells, including IGFs and fibroblast growth factors (FGFs), may also increase bone formation [19].

Along with increased bone formation, osteoblastic lesions are also associated with the stimulation of bone resorption [29]. Evidence of

increased osteolytic activity in metastatic prostate cancer is provided by significant increases in biochemical markers of bone resorption. In a recent study of patients with various cancers, urinary levels of the bone resorption marker N-telopeptide and serum levels of bone-specific alkaline phosphatase, a bone formation marker, were significantly higher in patients with osteoblastic lesions than in patients with osteolytic or mixed lesions [5]. Furthermore, the levels of these bone markers were significantly correlated with the number of skeletal sites involved in the metastases. However, even though osteoblastic lesions are associated with increases in both osteolysis and bone formation, the sites of bone resorption and bone deposition are uncoupled, meaning that the excessive new bone is deposited away from the sites of bone resorption, resulting in reduced bone strength and an increased risk for fractures and vertebral collapse [29].

Role of Bisphosphonates in the Treatment of Bone Metastases

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and have become an important class of drugs for the treatment of bone metastases. Clodronate, ibandronate (Boniva), pamidronate, and zoledronic acid have all been shown to significantly reduce skeletal morbidity in breast cancer patients with bone metastases [36]. Studies of zoledronic acid have also demonstrated long-term efficacy and safety in the treatment of patients with bone metastases secondary to prostate cancer, lung cancer, and a variety of other solid tumors [16–18].

Bisphosphonates are synthetic analogues of the pyrophosphate molecule and accumulate in the mineralized bone matrix at sites of active bone metabolism. First-generation bisphosphonates, etidronate and clodronate, resemble inorganic pyrophosphate and lack a nitrogen atom. Early nitrogen-containing bisphosphonates (N-BPs)—pamidronate, ibandronate, and alendronate (Fosamax)—have an aliphatic R² side chain containing a single nitrogen atom. Members of the newest generation of bisphosphonates, risedronate (Actonel) and zoledronic acid, contain heterocyclic R² side chains with one or two nitrogen atoms, respectively. Zoledronic acid is the only bisphosphonate containing two nitrogen atoms in an imidazole ring. N-BPs preferentially inhibit the mevalonate pathway, as discussed below.

POTENCY OF VARIOUS BISPHOSPHONATES

Bisphosphonates have been shown to inhibit bone resorption in a number of in vitro and in vivo preclinical models. Recent studies comparing the effectiveness of various bisphosphonates on bone resorption have demonstrated the increased potency of zoledronic acid compared with earlier-generation bisphosphonates [37]. Zoledronic acid was more potent than any other bisphosphonate tested in the inhibition of calcium release from mouse calvaria induced by 1,25-dihydroxyvitamin D₃, PTH, PTHrP, and recombinant human IL-1 β [37]. In addition, zoledronic acid was the most effective bisphosphonate in the reduction of serum calcium concentrations in thyroparathyroidectomized rats treated with 1,25-dihydroxyvitamin D₃ to induce hypercalcemia.

MECHANISM OF ACTION

Bisphosphonates may reduce bone resorption through several mechanisms, including induction of osteoclast apoptosis, inhibition of osteoclast maturation, and decreased osteoclast activity (Figure 3). During bone resorption, bisphosphonates are released and internalized by osteoclasts, thereby inhibiting their osteolytic activity and inducing apoptosis. First-generation bisphosphonates are metabolized by osteoclasts into nonhydrolyzable cytotoxic ATP analogues that accumulate and induce apoptosis [38].

In contrast, N-BPs exert their effects through inhibition of enzymes in the biosynthetic mevalonate pathway, leading to inhibition of the prenylation of GTP-binding proteins, including *ras*, *rho*, and *rac* [6, 39]. These signaling proteins are involved in cell proliferation, survival, membrane trafficking, and cytoskeletal organization and are necessary for osteoclast function. For example, treatment of isolated rat osteoclasts with alendronate resulted in their inability to form tight seal zones or ruffled borders because of a defect in intracellular vesicle transport, a process that requires protein prenylation [40]. Inhibition by N-BPs of farnesyl diphosphonate (FPP) synthase—an important enzyme in the mevalonate pathway—is of particular interest because the potency of various N-BPs with respect to FPP synthase inhibition in vitro correlates with their potency in the inhibition of bone resorption in vivo [41].

Inhibition of bone resorption by N-BPs may also occur through the inhibition of both osteo-

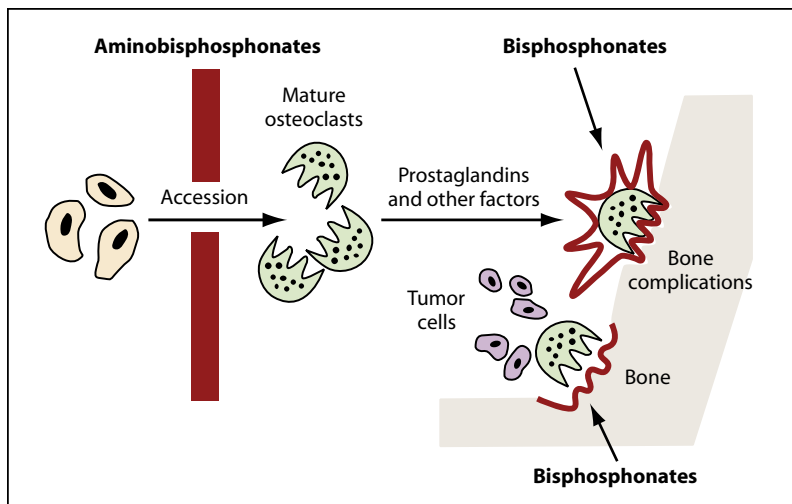


Figure 3 Proposed Mode of Action of Bisphosphonates

Bisphosphonates bind avidly to bone mineral around resorbing osteoclasts. Once released from the bone surface, bisphosphonates are internalized by osteoclasts, where they cause disruption of the biochemical processes involved in bone resorption. In addition, bisphosphonates may inhibit osteoclast maturation.

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clastogenesis and the recruitment of osteoclast progenitors to the bone. In vitro evidence demonstrates that N-BPs suppress bone resorption by directly affecting osteoclast precursors through a mechanism similar to that established for mature osteoclasts [7]. Furthermore, in vivo studies demonstrate that in osteoclast-deficient mice implanted with an osteoclastogenic sarcoma, pamidronate decreased the number of osteoclast myeloid precursor cells and the number of mature osteoclasts at the tumor site [8].

A potential mechanism for N-BP inhibition of osteoclastogenesis was suggested by in vitro studies demonstrating that pamidronate and zoledronic acid stimulate OPG production by primary human osteoblasts [42]. Increased production of OPG can interfere with the interaction of RANKL with RANK, its receptor on osteoclasts, thereby inhibiting the differentiation of osteoclast precursors into mature osteoclasts [28]. Recent evidence also suggests that N-BPs may have a direct effect on the proliferation and maturation of human osteoblasts by stimulating the differentiation of preosteoblastic cells [43].

PRECLINICAL ANTITUMOR ACTIVITY

Bisphosphonates have also demonstrated potent antitumor activity. In vitro studies show that bisphosphonates inhibit proliferation and induce apoptosis of a variety of human tumor cell lines,

including myeloma, breast cancer, and prostate cancer cell lines [9, 44, 45]. Exposure of myeloma cell lines and three specimens from myeloma patients to pamidronate or zoledronic acid resulted in a combination of cytostasis and apoptosis [9]. Similarly, clodronate, pamidronate, and zoledronic acid dose-dependently induced apoptosis in three different breast cancer cell lines, and pamidronate and zoledronic acid reduced the growth of three prostate cancer cell lines [44, 45].

Bisphosphonates have also demonstrated antitumor potential in animal models. Several mechanisms have been proposed, including direct antitumor effects, inhibition of bone resorption, and inhibition of tumor cell adhesion and invasion. As described previously, tumor cells secrete a variety of growth factors—including IL-6—that stimulate osteoclastic bone resorption, which, in turn, results in the release of several bone-derived growth factors, such as IGFs and FGFs. In vitro evidence has demonstrated that bisphosphonates inhibit the secretion of IL-6 from both myeloma cells and bone marrow stromal cells and reduce or block the stimulating effects of IGFs and FGF-2 on the growth of MCF-7 and T47D breast cancer cells [10, 46]. In addition, inhibition of bone resorption by bisphosphonates may decrease the amount of growth factors released from the bone matrix, resulting in a less-favorable environment for tumor proliferation.

Bisphosphonates have also been shown to inhibit tumor cell adhesion and invasion of the bone matrix [11]. After pretreatment with bisphosphonates, an in vitro Matrigel-based invasion assay demonstrated that both breast and prostate cancer cells failed to invade the bone extracellular matrix. This inhibition may be accomplished through inhibition of the proteolytic activity of MMPs, which are important for tumor cell invasion and migration. Bisphosphonates dose-dependently inhibit the activity of a broad range of MMPs produced by tumor cell lines, and this inhibition correlates with reduced invasion in the Matrigel assay [47]. Zoledronic acid was also shown to reduce the expression of MMP-2 and MMP-9 in PC-3 prostate cancer cells [12]. Furthermore, recent data suggest that integrin $\alpha_v\beta_3$ activity is modified by bisphosphonates. Zoledronic acid was shown to inhibit integrin $\alpha_v\beta_3$ -mediated adhesion of human umbilical vein endothelial cells and stimulated tumor necrosis factor-induced cell death [48]. Inhibition of integrin $\alpha_v\beta_3$ by bisphosphonates

may also interfere with osteoclast-mediated bone resorption because integrin $\alpha_v\beta_3$ is required for osteoclasts to adhere to the bone matrix [19].

Recent studies of animal models of multiple myeloma, breast cancer, and prostate cancer have demonstrated that N-BPs reduce tumor skeletal burden, supporting the antitumor data from in vitro studies [13, 14, 49]. In a murine model of multiple myeloma, treatment with pamidronate or zoledronic acid not only blocked myeloma-induced bone resorption but also inhibited myeloma cell growth and survival, resulting in reduced tumor burden compared with controls [49]. In a murine model of breast cancer, intracardiac injection of nude mice with human MDA-231 breast cancer cells resulted in osteolytic bone metastases. However, treatment of these mice with zoledronic acid significantly reduced the lesion area by more than 80% and reduced the number of osteoclasts present in bone lesions by almost 90%. Furthermore, zoledronic acid decreased the development of new bone metastases caused by inoculation of mice with 4T1 murine mammary cancer cells [14]. Zoledronic acid also decreased bone metastases and prevented reductions in bone mineral density in a murine model of prostate cancer in which athymic, hypogonadal, male nude mice were inoculated with the PC-3 prostate cancer cell line [13].

INSIGHTS FROM CLINICAL TRIALS

Recent clinical trials suggest that bisphosphonates may also delay disease progression in patients with advanced cancer metastatic to bone or in patients with nonmetastatic cancer [50, 51]. In a retrospective subset analysis of 74 patients with renal cell carcinoma and bone metastases who were enrolled in a randomized, multicenter study, zoledronic acid (4 mg via a 15-minute intravenous infusion) administered every 3 weeks for 9 months significantly delayed the median time to progression of bone lesions compared with placebo ($P = 0.014$) [50]. In an adjuvant trial, oral clodronate (1,600 mg) administered daily for 2 years to patients with operable breast cancer and no evidence of metastatic disease significantly reduced the development of bone metastases compared with placebo ($P = 0.016$), but only during the medication period [51].

Together, these preclinical and clinical data provide evidence that bisphosphonates not only inhibit bone resorption induced by bone metas-

tases but may also potentially delay disease progression by preventing the progression of existing bone metastases or the occurrence of new bone metastases in patients with advanced cancers.

Summary and Conclusions

Bone metastases represent a source of significant skeletal morbidity for patients with a variety of cancers, and bisphosphonates are now standard treatment for the clinical management of bone metastases. Primary cancer cells metastasize through a complex process that involves CAMs and proteolytic enzymes detaching from the primary tumor, entering the vasculature, migrating to distant bone capillaries, exiting the vasculature, and adhering to the endosteal surface of the bone. The mineralized bone matrix and the bone marrow contain a variety of growth factors and cytokines that are released into the microenvironment during bone remodeling, providing a favorable environment for the growth of tumor cells.

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption. These agents bind to the bone matrix and are released and internalized by osteoclasts during bone resorption. First-generation bisphosphonates inhibit osteoclast activity primarily by inducing osteoclast apoptosis, whereas N-BPs affect biochemical pathways through the inhibition of protein prenylation. This process leads to inactivation of signaling molecules, resulting in interference with osteoclast activity and survival.

Bisphosphonates have been shown to reduce bone resorption and increase bone density in a number of in vitro and in vivo preclinical trials, with zoledronic acid demonstrating increased potency compared with earlier-generation compounds. Bisphosphonates are routinely used for the prevention of skeletal complications resulting from tumor-induced bone destruction in patients with bone metastases. However, the role of bisphosphonate therapy in the treatment of cancer patients continues to evolve. Preclinical studies suggest that bisphosphonates not only inhibit osteoclast-induced bone resorption but also may have direct effects on tumor progression. In vitro and in vivo studies demonstrate that bisphosphonates induce apoptosis of tumor cells, and several murine models of cancer show that bisphosphonate treatment results in decreased skeletal tumor burden. In addition, inhibition of osteolysis may also result in antitumor activity by inhibiting

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the release of growth factors in the bone micro-environment. Clinical trials will investigate the potential role of bisphosphonates in the prevention of bone metastases. Therefore, bisphospho-

nates may one day play a role in the delay of disease progression and become an essential therapy for cancer patients throughout the entire course of their disease.

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PEER VIEWPOINT

Commentary by James R. Berenson, MD

During the past decade, there has been a tremendous increase in our understanding of the biology and treatment of metastatic bone disease. The 1990s were a period during which the efficacy of intravenously administered bisphosphonates in preventing skeletal complications was clearly demonstrated for patients with lytic bone disease from two specific cancers—breast cancer and multiple myeloma [1, 2]. However, studies with weaker bisphosphonates, such as pamidronate, failed to show benefits for patients with other tumor types that metastasized to bone [3]. Simultaneously, data were generated showing the ability of oral bisphosphonates to improve bone density and reduce the risk of fractures among patients with osteoporosis from benign causes. Data began to emerge demonstrating the potential antitumor effects of these drugs in both in vitro and in vivo preclinical studies [4, 5].

The new millennium has expanded the use of these agents, particularly zoledronic acid [Zometa], to all kinds of patients with metastatic bone disease, regardless of the site of the primary cancer and type of bone metastasis—lytic, blastic, or mixed—based on the results of three large, recently published, randomized clinical trials [6–8]. Although these studies showed a reduction of skeletal complications with chronic use of this agent, an impact of zoledronic acid at the currently used dose (4 mg) on overall survival was not observed. However, anecdotal reports and analysis of some subsets of patients from these studies and other clinical trials showed

an improvement in survival with the addition of bisphosphonates to the patients' other antitumor therapy [9].

ANTITUMOR POTENTIAL

Because zoledronic acid demonstrates not only the most potent anti-bone resorptive effects but also antitumor effects as well in preclinical studies [10], clearly showing an antitumor effect clinically is likely to be better with this agent than with other bisphosphonates. Early phase I trials involving administration of zoledronic acid, given rapidly at higher doses, suggested an antitumor effect of this agent but were limited by untoward effects on renal function. Ongoing studies are evaluating higher doses of zoledronic acid given more slowly, with the expectation of using these doses in future trials to evaluate the antitumor effects of this agent.

It is important to recognize that the concentrations of zoledronic acid or any other bisphosphonate are unlikely to be high enough outside the bone and bone marrow environment to have an antitumor effect that is clinically significant. Nevertheless, recent studies showing the ability of both pamidronate and zoledronic acid to stimulate antitumor T cells suggest the existence of alternative mechanisms by which these drugs may achieve their antitumor effects without being present in the local tumoral environment [11].

PREVENTING METASTATIC BONE DISEASE

Much interest has been generated in using bisphosphonates to prevent the development

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Two other peer viewpoints by Drs. Robert Dreicer and E. David Crawford appear on pages 216 and 219.

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of metastatic bone disease altogether, but the results have been disappointing. Although an initial randomized study suggested that oral clodronate administered to women with operable breast cancer was beneficial in reducing bone and nonosseous metastases and improving overall survival [12], another study showed no benefit to this treatment [13]. Whether these disappointing results stem from the weaker oral agent evaluated or the small size of the trials will hopefully be answered through ongoing larger randomized clinical studies evaluating a variety of bisphosphonates in this clinical setting. There have been concerns that chronic use of bisphosphonates would “push” the tumor from the bone into more ominous metastatic sites, but this has not occurred with widespread use of these agents among patients with a variety of tumor types.

Recent preclinical studies have suggested synergistic antitumor effects when zoledronic acid is combined with a variety of chemotherapeutic agents, hormonal therapy, glucocorticoids, and tyrosine kinase inhibitors. Specifically, the synergistic antileukemic effects of the combination of zoledronic acid and imatinib (Gleevec) on chronic myelogenous leukemia cells provide the rationale for a clinical trial with this combination in this bone marrow-based cancer. Moreover, the lack of obvious lytic or blastic bone involvement in most of these patients would also help separate this bisphosphonate’s antitumor potential from its anti-bone resorptive effects, which becomes complicated in other bone-marrow-based malignancies with frequent bony involvement, such as multiple myeloma.

REVERSING BONE LOSS

Another increasingly recognized clinical problem is cancer treatment-induced bone loss. Among cancer patients treated with androgen blockade, ovarian ablation, aromatase inhibitors, and glucocorticoids, bone loss is significant, even in the absence of metastatic bone disease [14]. Recent studies show that zoledronic acid can reverse bone loss and actually improve bone density for patients undergoing androgen blockade for the treatment of localized prostate cancer [15], as well as in women receiving aromatase inhibitors for breast cancer.

It is likely that this improvement in bone density will be clinically beneficial for these kinds of

cancer patients, given the results of trials showing that an improvement in bone density is associated with a reduction in fracture risk for patients without cancer who are receiving chronic bisphosphonate therapy for other conditions associated with bone loss. In addition, the large population of individuals with monoclonal gammopathy of undetermined significance has recently been shown to be at high risk of developing fractures, especially of the vertebral bodies. As a result, a clinical trial has started to determine whether intermittent use of zoledronic acid can improve bone density for these patients and help reduce their high fracture risk.

NEW CLASSES OF DRUGS

The recent discovery of a variety of specific cytokines and other proteins that lead to bone resorption has led to the development of new classes of potential drugs to help improve the lives of cancer patients with both metastatic bone disease, as well as those with bone loss without bone involvement. Inhibitors of the RANKL-RANK signaling pathway are being tested in early clinical trials, with promising preliminary results. Preclinical studies also show an antitumor effect of these agents [16]. These biologic agents have the potential to help improve upon the results already demonstrated with bisphosphonate therapy. It will be important to determine whether these new agents can be combined with bisphosphonates to more effectively reduce skeletal complications, as well as overall tumor burden, in patients with cancer. This will hopefully achieve the ultimate goal of both improving the quality of life and overall survival of cancer patients with bone-related disease.

James R. Berenson, MD
Medical and Scientific Director
Institute for Myeloma and Bone Cancer Research
Los Angeles, California

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PEER VIEWPOINT

The Role of Bisphosphonates in Prostate Cancer: When You Get to the Fork in the Road, Take It

Commentary by Robert Dreicer, MD, FACP

Dr. Lipton has crafted a thoughtful and clinically relevant overview of both the pathophysiology of bone metastases and the mechanisms of action of bisphosphonates. As highlighted in this review, there are a staggering number of patients worldwide with epithelial and hematologic neoplasms impacted by the development of bone metastases at some point during the course of their disease. The toll both in human suffering and economic costs from the consequences of bone metastases is incalculable.

Interest in the physiology of bone metastases has been long-standing. The “seed and soil” hypothesis was first proposed in the late 1800s, when Paget theorized that there was some-

thing about metastatic sites that promoted cancer cell growth. Subsequent work by such notables as James Ewing and in the modern era Isaiah Fidler has further defined concepts of the microenvironment. Recent work by many investigators has focused on the impact of stroma (fibroblasts, endothelial and inflammatory cells, and the extracellular matrix) on micrometastatic cell growth and development. The family of cell-surface-receptor integrins, which are composed of non-covalently associated alpha and beta subunits, is believed to play a major role in mediating both cell-cell and cell-matrix interactions and may ultimately be a therapeutic target for new drug development.

BISPHOSPHONATES IN PROSTATE CANCER

Bisphosphonates are effective inhibitors of osteoclast-mediated bone resorption and have demonstrated activity in a variety of clinical settings, including the management of osteolytic

bone metastases from breast cancer and multiple myeloma. In contrast to these neoplasms, which demonstrate primarily lytic bone metastases, it has been far more difficult to demonstrate the utility of bisphosphonates in prostate cancer. Although bone metastases from prostate cancer are typically osteoblastic, there is evidence suggesting that osteoblastic lesions are associated with increased osteolysis, and bone resorption markers are significantly elevated in patients with advanced prostate cancer [1, 2]. Several relatively small trials of first- and second-generation bisphosphonates, including clodronate, alendronate (Fosamax), and pamidronate, have reported some efficacy in improving bone pain from metastatic prostate cancer [3]. Recently, two well-powered, randomized trials assessing the utility of pamidronate and the third-generation bisphosphonate zoledronic acid have been reported.

Small and colleagues [4] reported on the pooled results of two multicenter, double-blind, randomized, placebo-controlled trials comparing pamidronate with placebo on pain control in patients with metastatic prostate cancer. More than 350 patients with androgen-independent metastatic prostate cancer and bone pain were randomized to receive 90 mg of pamidronate or placebo every 3 weeks. Additional therapy, including external-beam radiotherapy, radiopharmaceuticals, second-line hormonal therapy, and chemotherapy, was allowed following randomization. There were no significant differences between the two groups in self-reported pain measurements, analgesic use or skeleton-related events (SREs; pathologic fracture, irradiation or surgery to bone, spinal cord compression, or hypercalcemia).

In contrast to the findings with pamidronate, Saad et al [5] conducted a phase III double-blind trial comparing two doses (8 mg and 4 mg) of zoledronic acid with placebo in more than 600 patients with androgen-independent metastatic prostate cancer and known bone metastases. At the 4-mg dose, zoledronic acid decreased the number of SREs (defined as pathologic fracture, spinal cord compression, surgery or radiotherapy to bone, or changes in antineoplastic therapy to treat bone pain) when compared with placebo. Although therapy at the 4-mg dose was well tolerated, the 8-mg dose was found to have an unacceptable rate of renal insufficiency,

and patients randomized to this arm were subsequently treated with 4 mg. On the basis of the results from this study, zoledronic acid was awarded a clinical indication by the Food and Drug Administration (FDA) for use in patients with androgen-independent prostate cancer and evidence of bone metastases.

PLACING THE DATA IN PERSPECTIVE

This FDA approval begs the question should bisphosphonates be used routinely in all patients with androgen-independent prostate cancer metastatic to bone? How clinically significant is the benefit provided by zoledronic acid? What are the optimal dose, frequency and total duration of therapy? What is the economic impact of adding bisphosphonates to current therapies?

Although the study by Saad et al was well designed and demonstrated a statistically significant reduction in SREs in patients treated with the 4-mg dose, some observers have questioned the differences in response rates in the two arms receiving zoledronic acid: For instance, why were the results with patients who developed an SRE in the group started at 8 mg and dropped to 4 mg closer to the placebo results than those in the 4-mg arm? They also questioned the impact of a significant dropout rate at 1 year in all three arms. An additional concern was whether the negative impact on quality of life from the side effects attributed to zoledronic acid (nausea, dizziness, fever, myalgia and lower extremity edema, which were more commonly seen in patients receiving zoledronic acid than in those receiving placebo) offset the benefit from decreasing SREs [6, 7].

Despite the evidence from the study by Saad et al, which administered zoledronic acid on an every-3-week schedule, my own observations and informal discussions with colleagues in the community suggest that this agent is typically administered on an every-4-week schedule. There is no guidance from the current study regarding the optimal duration of therapy. Should therapy be stopped after an SRE or administered for the remainder of the patient's life?

Are we adding another drug into the increasingly common scenario of the prostate cancer patient and family in conflict with hospice caregivers in debating the need for ongoing luteinizing hormone-releasing hormone agonist therapy?

Reed et al recently reported an analysis of the cost-effectiveness of zoledronic acid on the pre-

*A third peer viewpoint
by Dr. E. David
Crawford appears
on page 219.*

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vention of skeletal complications using data from the randomized trial by Saad et al [5]. Although they determined that the average total cost of medical care in patients with one or more SREs was \$3,342 higher than that in those who did not have an SRE, there was no statistically significant savings in the cost of medical care in patients receiving zoledronic acid vs placebo [8].

When it comes to making evidence-based judgments regarding the role of bisphosphonates in patients with androgen-independent metastatic prostate cancer, there are many more questions than answers. We are finally approaching the end of the beginning of the road toward understanding the physiology of bone metastases, and now we need to concentrate on optimizing current therapies while working on the next generation of agents that can further decrease the suffering of patients with bone metastases.

Robert Dreicer, MD, FACP
Professor of Medicine
Cleveland Clinic Lerner College of Medicine
Director, Genitourinary Medical Oncology
Associate Director, Experimental Therapeutics
Taussig Cancer Center
Cleveland Clinic Foundation
Cleveland, Ohio

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P E E R V I E W P O I N T

Third-Generation Bisphosphonates: A New Area of Clinical Interest

Commentary by E. David Crawford, MD

Bone metastases are common in a number of cancers, including the most frequently diagnosed cancers in men and women: lung, breast, and prostate. Additionally, bone metastases occur in thyroid and renal cancers as well as melanoma and myeloma. In general, bone metastases signal an incurable lesion, and treatment is therefore palliative. In the past decade, we have gained a new understanding of the complex interaction that occurs in the bone when metastases occur. We also have witnessed progress in the therapeutic intervention both to delay the progression of bone disease and perhaps even delay its onset.

Dr. Lipton provides a comprehensive review

of the pathophysiology behind bone metastases. This knowledge has led to the development and understanding of third-generation bisphosphonates. Studies [1,2] in metastatic breast cancer and myeloma have suggested that bisphosphonates are pyrophosphate analogs that bind weakly to osteoclasts and the hydroxyapatite component of bone. In the bony milieu, bisphosphonates interfere with the mevalonic acid biosynthesis pathway, which is critical for intracellular signaling of the osteoclast. This leads to osteoclast dysfunction and apoptosis. Bisphosphonates containing nitrogen seem to be the most potent.

Men with advanced prostate cancer are treated with androgen deprivation. This treatment leads to the development of osteoporosis and subsequent pathologic fractures. Men with hormone-refractory disease have bone metastases in more than 80% of cases [3]. These bone

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metastases can be a source of significant skeleton-related events, such as fractures, spinal cord compression, need for surgery or irradiation to bone, and change in antineoplastic therapy secondary to bone pain.

In a landmark study by Saad and colleagues [4], zoledronic acid (Zometa) was compared with placebo in 643 patients with hormone-refractory prostate cancer. The number of patients who suffered skeleton-related events was significantly smaller in the zoledronic acid arm than in the placebo arm (44% vs 33%, $P = 0.02$). There was a trend to improve survival, although it was not statistically significant. Many clinicians mistakenly believe that osteoblastic metastases are nonthreatening. Osteoblastic metastases represent abnormal bone formation and are subject to skeleton-related events.

As outlined by Dr. Lipton, the bisphosphonates have opened a new area of clinical interest in a number of advanced cancers. Some studies [5] suggest that some of the third-generation bisphosphonates may have antineoplastic behavior in vitro and in vivo. Administered intravenously, the new nitrogen-containing bisphosphonate, zoledronic acid, is well tolerated and an effective treatment for both osteolytic and blastic bone

metastases. In a number of cancers, bisphosphonates are being studied earlier in the disease to determine whether bone metastases can be delayed or prevented. Several phase III trials examining this important question are ongoing.

E. David Crawford, MD
Professor of Surgery and Radiation Oncology
Head, Section of Urologic Oncology
University of Colorado Cancer Center
Denver, Colorado

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