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REVIEW ARTICLE

Skeletal complications of prostate cancer: Pathophysiology and therapeutic potential of bisphosphonates

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Abstract
Patients with prostate cancer are at risk for skeletal complications resulting from treatment-induced bone loss and for bone metastases. The therapeutic potential of zoledronic acid for the treatment of prostate cancer has been demonstrated in both preclinical and clinical studies. In patients receiving androgen-deprivation therapy, zoledronic acid increases bone mineral density, and, in patients with bone metastases, it reduces the incidence of skeletal complications. Preclinical studies have also demonstrated the antitumor potential of bisphosphonates. Specifically, zoledronic acid inhibits proliferation and induces apoptosis of human prostate cancer cell lines in vitro and has enhanced antitumor activity when combined with taxanes. Animal models have further shown that bisphosphonates decrease tumor-induced osteolysis and reduce skeletal tumor burden. In a model of prostate cancer, zoledronic acid significantly inhibited growth of both osteolytic and osteoblastic tumors and reduced circulating levels of prostate-specific antigen. These studies suggest that zoledronic acid has the potential to inhibit bone metastasis and bone lesion progression in patients with prostate cancer.

Key Words: *Antitumor, prostate cancer, zoledronic acid*

Introduction

Prostate cancer is the most commonly diagnosed malignancy in men. Worldwide, approximately 540,000 men are diagnosed with prostate cancer annually, and more than 200,000 deaths result from prostate cancer annually [1]. Although treatment for advanced prostate cancer is rarely curative, the disease typically has a long natural history, and current treatment strategies delay disease progression for many years. Consequently, patients with advanced prostate cancer live with their disease for extended periods of time, during which they are at risk of developing skeletal complications. One of the most significant clinical challenges in the management of prostate cancer is maintaining bone health. Patients with prostate cancer are at risk for skeletal morbidity from a variety of causes, including age-related bone loss, bone loss caused by androgen ablation, and tumor-induced osteolysis associated with bone metastases. Long-term androgen-deprivation therapy (ADT) in patients without bone metastases results in significant bone loss, osteoporosis, and an increased risk of fractures. This problem is further compounded by bone metastases, which develop in 65% to 75% of patients at some point during the course of their disease [2]. Bone metastases cause severe bone pain that often requires strong analgesics or palliative radiation therapy and further increase the risk of pathologic fractures and spinal cord compression.

Until recently, however, the risk of skeletal complications in men with prostate cancer had not been fully appreciated and the available treatment options have been limited. Although bisphosphonates had been shown to palliate bone pain to some degree, they had not demonstrated objective clinical benefits in patients with bone metastases. Recently, however, clinical studies have shown that bisphosphonates can effectively maintain bone health and minimize skeletal morbidity in patients with prostate cancer. But, only zoledronic acid in well-controlled, randomized clinical trials has been shown to significantly increase bone mineral density (BMD) in patients receiving

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ADT and to significantly reduce the incidence of skeletal complications among patients with bone metastases. Preclinical studies have also shown that zoledronic acid has antitumor effects on prostate cancer cell lines and in animal models of human prostate cancer, suggesting that the clinical benefit of zoledronic acid may extend beyond prevention of bone loss and skeletal complications. This review will focus on the preclinical and clinical activity of zoledronic acid in prostate cancer and its role in the management of bone health throughout the treatment continuum.

Cancer treatment-induced bone loss

Cancer treatment-induced bone loss (CTIBL) represents a significant clinical problem in patients with prostate cancer, adding to the fact that many prostate cancer patients present with low BMD already at the initial cancer diagnosis [3]. Androgen-deprivation therapy by either surgical or chemical castration with or without an antiandrogen has become the standard treatment for patients with increasing prostate-specific antigen (PSA) levels after definitive local therapy [4]. Although ADT is highly effective at suppressing tumor growth and delaying disease progression, therapies that suppress androgen signaling accelerate bone loss and increase the risk of pathologic and nonpathologic fractures [5,6]. Rates of bone loss reported during initial ADT in men with prostate cancer are as high or higher than those reported in postmenopausal women [7]. One small study showed that among patients who received ADT for at least 12 months 46% had osteopenia, 38% had osteoporosis, and 50% had vertebral fractures [8]. Moreover, the presence of vertebral fractures was significantly correlated with reduced BMD ($P = .001$). Two recent chart review studies have reported similar results [9,10]. In a review of 3,887 men with nonmetastatic prostate cancer who received ADT compared with 7,774 men with nonmetastatic prostate cancer who did not, treatment with ADT significantly increased fracture risk by 40% after <1 year of therapy and by 50% after >3 years of therapy ($P < .001$) [9].

Significant increases in bone resorption associated with ADT have also been demonstrated through measurement of biochemical markers of bone metabolism [11,12]. In a study of 15 prostate cancer patients with castrate levels of testosterone as a result of treatment with a gonadotropin releasing hormone (GnRH) agonist, the BMD of the total hip decreased significantly compared with controls after 12 months of treatment ($P < .001$), and this was associated with a significant increase in urinary excretion of N-telopeptide (a marker of bone resorption) after six and 12 months of treatment (Figure 1) [12].

Preclinical models of bone loss

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and have been shown to prevent bone loss in ovariectomized animals. These models are representative of bone loss associated with either estrogen or androgen ablation. In ovariectomized animals that normally exhibit profound bone loss, zoledronic acid has been shown to preserve bone mass, architecture, and strength [13–15]. In ovariectomized rats, weekly SC injections of zoledronic acid (0.3, 1.5, or 7.5 μg/kg/week) for one year completely preserved bone mineral density and maintained the mechanical strength of the femur and vertebrae [15,16]. Similarly, long-term treatment of ovariectomized adult rhesus monkeys with zoledronic acid (0.5, 2.5, or 12.5 μg/kg/week SC) for 69 weeks dose-dependently decreased bone turnover and bone loss without adversely affecting bone quality [13,17–19].

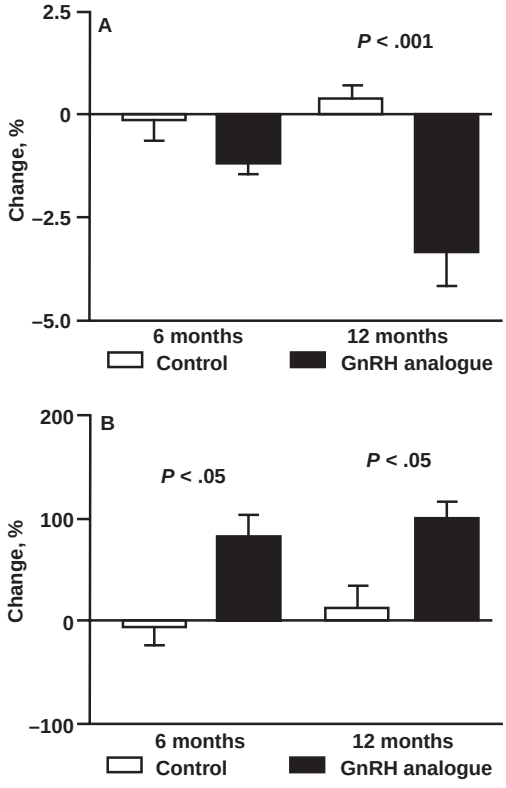

Figure 1. Percent change from baseline in (A) bone mineral density (BMD) of the total hip and (B) urinary excretion of N-telopeptide after 6 and 12 months of androgen-deprivation therapy compared with controls. Adapted with permission from Mittan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JM. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J Clin Endocrinol Metab 2002; 87: 3656–61 [12]. *Copyright 2002, The Endocrine Society*.

Prevention of CTIBL in patients with prostate cancer

Consistent with these preclinical data, zoledronic acid (4 mg every 3 months) was recently shown to prevent bone loss in men with nonmetastatic prostate cancer receiving ADT [3]. Patients in this study (N = 106) were receiving initial treatment with a GnRH agonist with or without an antiandrogen. At one year, patients treated with zoledronic acid had a 5.6% increase in BMD of the lumbar spine compared with baseline and significantly greater BMD compared with the placebo group ($P < .001$), which exhibited substantial bone loss (2.2% decrease from baseline) after one year of ADT (Figure 2) [3]. Patients in the placebo group who were treated with a GnRH agonist plus an antiandrogen had the most profound bone loss (–2.7%), but also received the greatest benefit from treatment with zoledronic acid (+7.0%). By comparison, pamidronate (60 mg every 3 months) has been shown to prevent bone loss in patients with prostate cancer receiving ADT, but did not increase BMD above baseline [20]. These studies have important implications with respect to maintaining bone health and reducing fracture risk in patients with prostate cancer receiving ADT. Maintaining bone health should improve quality of life for these patients and may delay the development of bone metastases. More importantly, correlative studies suggest that reducing skeletal complications, particularly fractures, may provide an indirect survival benefit in men with prostate cancer [21].

Bone metastases

Prostate cancer typically forms osteoblastic lesions that are characterized by increased formation of new woven bone of poor quality, but these lesions are also associated with significant increases in tumor-induced osteolysis as evidenced by high levels of bone resorption markers [22,23]. Therefore, patients with bone metastases from prostate cancer are at risk for fractures and other skeletal complications. A recent study of bone resorption markers in patients with bone metastases from prostate cancer demonstrated a correlation between high levels of bone resorption markers and an increased risk of skeletal complications. Patients with high levels of N-telopeptide (>100 nmol/mmol creatinine) had a five-fold increased risk of skeletal complications compared with patients with low N-telopeptide levels (<50 nmol/mmol creatinine) [24].

As a result of excess osteolysis, patients with bone metastases from prostate cancer suffer a variety of skeletal complications (Table I) [25–27]. The placebo arm of the recent randomized trial of zoledronic acid provides the most comprehensive data on skeletal complications occurring in prostate cancer patients [28]. After 24 months of follow-up, half of the patients in the placebo arm had at least one skeletal complication, which was defined as a pathologic fracture, radiation or surgery to bone to palliate bone pain or to prevent or treat pathologic fractures, spinal cord compression, hypercalcemia of malignancy, or a change in antineoplastic therapy to treat

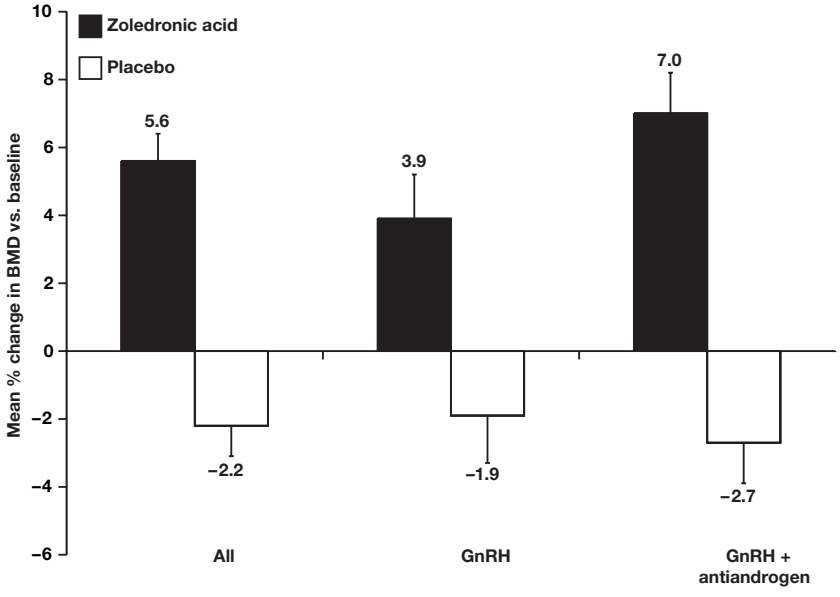

Figure 2. Mean percent change from baseline bone mineral density (BMD) of the lumbar spine after 1 year for patients treated with zoledronic acid or placebo. Adapted with permission from Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol 2003; 169: 2008–12 [3].

Table I. Percentage of Placebo-Treated Patients With at Least 1 Skeletal Complication After the Indicated Length of Follow-up in Phase III Trials

Skeletal event	Patients affected,%		
	Prostate (24 months)†	Breast (24 months)‡	Lung and OST (21 months)§
Any skeletal event*	49	64	46
Radiation to bone	33	43	34
Pathologic fracture	25	52	22
Surgery to bone	4	11	5
Spinal cord compression	8	3	4
Change in antineoplastic therapy for pain	7	—	—
Hypercalcemia of malignancy	1	13	4

OST = Other solid tumors (other than breast or prostate cancer).
*Not including hypercalcemia of malignancy.
†Data from Saad et al.[25].
‡Data from Lipton et al.[26].
§Data from Rosen et al.[27].

pain [28]. The incidence of skeletal complications in patients with prostate cancer was lower than the incidence observed in patients with breast cancer but similar to the incidence observed in patients with bone metastases from lung cancer [25–27]. The most common skeletal complications were radiation to bone and pathologic fractures regardless of the underlying malignancy. Bone pain is a particular therapeutic challenge in patients with bone metastases from advanced prostate cancer. Moreover, patients with prostate cancer enrolled in this trial had a mean of 1.5 skeletal events per year [28], and, considering that half of the patients had no skeletal complications, those who did have an event had a mean of approximately three events per year. Therefore, over the course of their disease patients may suffer multiple skeletal complications, which can reduce quality of life and may adversely affect survival [29].

Role of bisphosphonates in patients with bone metastases

Bisphosphonates have been investigated primarily for the palliation of bone pain in patients with bone metastases from prostate cancer, and several small, placebo-controlled studies with clodronate and etidronate have demonstrated transient decreases in bone pain but no significant benefit compared with placebo [30–33]. More recently, larger, randomized, placebo-controlled trials of oral clodronate and IV pamidronate have also failed to demonstrate any statistically significant decrease in bone pain compared with placebo [34,35], and these trials failed to demonstrate any objective clinical benefits in terms of a reduction in the incidence of skeletal complications [35] PSA response [34], or delay in time to symptomatic bone lesion progression [36]. In contrast, zoledronic acid has demonstrated long-term objective clinical benefits compared with placebo in patients with bone metastases from advanced prostate cancer [28,37]. In this large, multicenter, randomized trial, zoledronic acid significantly reduced the incidence and delayed the onset of skeletal complications and reduced bone pain compared with placebo throughout the two-year treatment period (Table II) [28]. The statistically significant benefits of zoledronic acid in this patient population, in which other bisphosphonates have not demonstrated similar benefit, may be a result of its greater pharmacologic activity. Zoledronic acid has been shown in preclinical models to potently inhibit tumor-induced osteolysis and tumor cell growth and metastasis more effectively and at lower concentrations than other bisphosphonates.

Preclinical antitumor effects

The effects of bisphosphonates on tumor-induced osteolysis have been studied in murine models of mammary tumors and multiple myeloma [38–40]. These studies have shown that bisphosphonates effectively inhibit tumor-induced osteolysis thus reducing the release of bone-derived growth factors that can stimulate tumor growth in bone.

In addition to their effects on tumor-induced osteolysis, there is now extensive preclinical evidence that bisphosphonates have direct antitumor activity against a variety of human tumor cell lines in vitro [41–50], including several prostate cancer cell lines [51,52], and bisphosphonates inhibit tumor growth in animal models. Bisphosphonates appear to also inhibit tumor cell adhesion and invasion of the extracellular bone matrix [53–56], and zoledronic

Table II. Clinical Benefit of Zoledronic Acid in Patients With Bone Metastases From Prostate Cancer

Clinical endpoint	Zoledronic acid 4 mg (n = 214)	Placebo (n = 208)	*P* value
Patients with an SRE,*%	38	49	.028
Median time to first SRE, days	488	321	.009
Mean skeletal morbidity rate, SREs/year	0.77	1.47	.005
Multiple event analysis, risk ratio	0.640		.002
BPI composite pain score at 24 months	0.58	1.05	.024

SRE = Skeletal-related event; BPI = Brief Pain Inventory.
Data from Saad et al. [28].

acid and other bisphosphonates have demonstrated antiangiogenic activity [57,58]. Therefore, bisphosphonates have the potential to reduce skeletal tumor burden via several direct antitumor mechanisms.

Prostate cancer cell lines

In vitro studies with several different prostate cancer cell lines (i.e. LNCaP, PC-3, and Du145) have shown that zoledronic acid inhibits proliferation, reduces cell viability, induces apoptosis, and causes cell-cycle arrest of prostate cancer cell lines in a dose-dependent fashion and at significantly lower concentrations than pamidronate (Figure 3) [51,52,59]. In one study, zoledronic acid (340 μM) inhibited proliferation of PC-3 and LNCaP cells by up to 70% after 4 days, and at a concentration of 68 μM zoledronic acid induced apoptosis and caused cell-cycle arrest [51]. The androgen-independent PC-3 cell line, which lacks functional p53, underwent rapid apoptosis and cell-cycle arrest in S phase, whereas androgen-dependent LNCaP cells with wild-type p53 exhibited a more delayed apoptotic response and underwent G_1 phase arrest. Therefore, the status of p53 in prostate tumor cells appears to influence the response of prostate tumor cells to zoledronic acid. In a more physiologic culture system using bone marrow stromal cells to mimic the normal microenvironment of prostate tumors growing in bone, zoledronic acid potently inhibited colony formation by prostate cancer cell lines [60].

Synergistic antitumor effects in vitro

In vitro studies have also shown that the combination of zoledronic acid with standard anticancer drugs, including taxanes, results in synergistic apoptotic effects on a variety of tumor cell lines [61,62]. For example, the combination of zoledronic acid (10 μM) plus paclitaxel (2 nM) resulted in a fourfold enhancement in apoptosis of MCF-7 breast cancer cells compared with either agent alone [61]. Similarly, the combination of low concentrations of zoledronic acid (12.5 or 25 μM) plus subtherapeutic concentrations of docetaxel (<1 ng/mL) demonstrated additive and dose-dependent effects on the viability of PC-3 prostate cancer cells [63]. These preclinical findings have important implications in light of recent results from randomized, phase III trials showing that docetaxel-based regimens confer a survival advantage in patients with hormone-refractory prostate cancer [64,65].

Animal models of prostate cancer

These in vitro findings are supported by data from animal models showing that bisphosphonates have antitumor effects in vivo [39,40,43,51,66–69]. These studies have focused primarily on models of multiple myeloma, breast cancer, and prostate cancer, and have shown that bisphosphonates can inhibit the formation or progression of bone metastases and/or reduce skeletal tumor burden. These effects are observed when the bisphosphonate is administered either at the time of tumor cell inoculation (i.e. prevention setting) or after bone metastases are established (i.e. treatment setting). Data were recently reported from a prostate cancer model in which PC-3 or LuCaP 23.1 cells were injected directly into the tibiae of SCID mice [51]. In this model, PC-3 cells form osteolytic lesions whereas LuCaP cells form osteoblastic lesions, which are more typical of human prostate cancer. The treatment group received zoledronic acid (5 μg SC twice weekly) either at the time of tumor cell injection or after tibial tumors were established (7 days for PC-3 and 33 days for LuCaP tumors). In this model, zoledronic acid significantly inhibited growth of both osteolytic and osteoblastic metastases compared with untreated control mice as evidenced by radiographic analysis [51]. In animals injected with either cell line, skeletal tumor volume was significantly reduced in both the prevention and treatment settings (Figure 4) [51]. Therefore, zoledronic acid reduces skeletal tumor burden associated with both osteolytic and osteoblastic lesions. In animals injected with LuCaP cells, zoledronic acid also significantly decreased serum levels of PSA

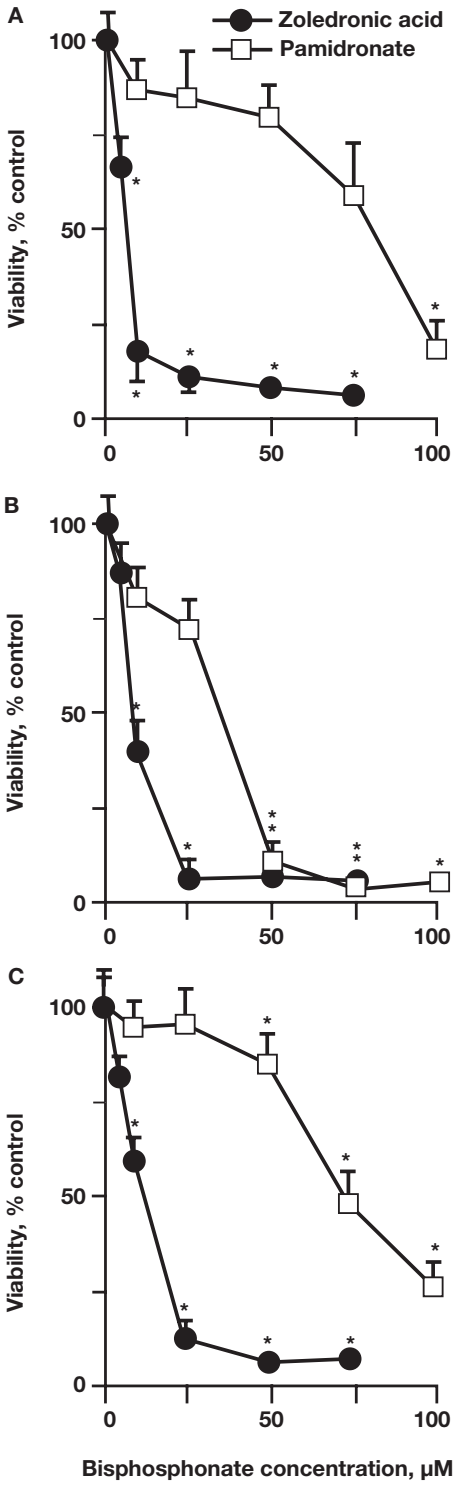

Figure 3. Effects of zoledronic acid and pamidronate on viability of (A) LNCaP, (B) PC-3, and (C) DU145 human prostate cancer cell lines. *Indicates statistically significant reductions from baseline ($P < 0.001$). Adapted with permission from Oades GM, Senaratne SG, Clarke IA, Kirby RS, Colston KW. Nitrogen containing bisphosphonates induce apoptosis and inhibit the mevalonate pathway, impairing Ras membrane localization in prostate cancer cells. J Urol 2003; 170: 246–52 [59].

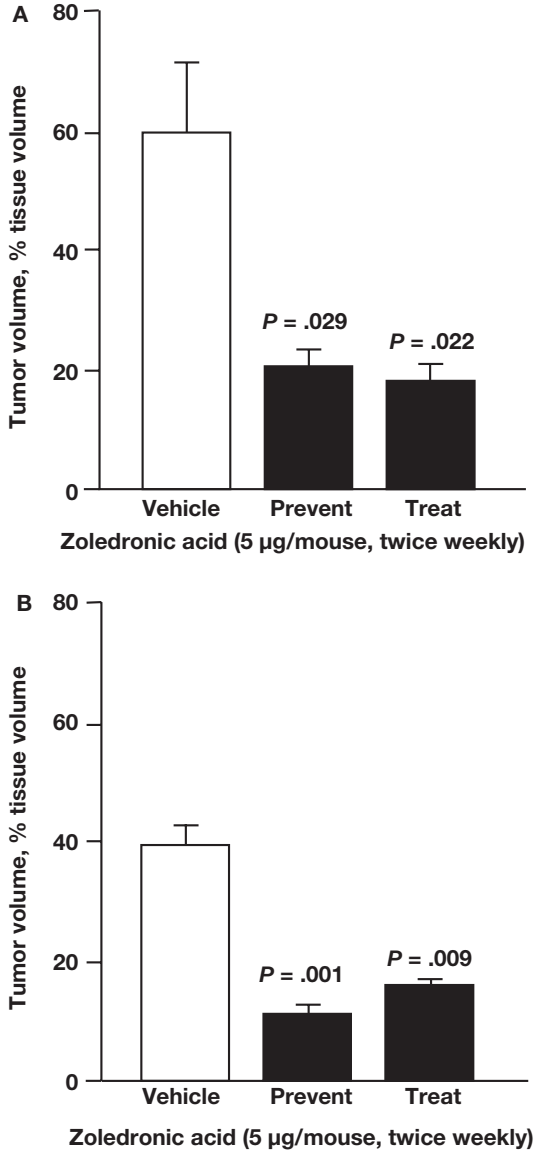

Figure 4. Bone tumor volume in severe combined immunodeficient mice bearing either (A) osteolytic PC-3 or (B) osteoblastic LuCaP 23.1 human prostate cancer cells. Mice were treated with vehicle control or zoledronic acid (5 μg SC twice weekly) either at the time of tumor cell injection (i.e. prevention) or after tumors were established (i.e. treatment). Adapted with permission from Corey et al. [51].

in both the prevention ($P = .02$) and treatment ($P = .01$) settings [51]. These in vivo preclinical studies provide compelling evidence of the potential of zoledronic acid to reduce skeletal tumor burden and inhibit formation and progression of bone metastases associated with prostate cancer. This could have important implications with respect to the clinical benefit of zoledronic acid in patients with prostate cancer. However, to date, clinical studies in advanced prostate cancer have not shown a significant effect of bisphosphonates on tumor progression in bone or overall survival compared with placebo.

Prevention of bone metastases

The potential of zoledronic acid to prevent bone metastasis has also been elegantly demonstrated in an animal model of prostate cancer [70]. In this model, mice were injected intracardially with PC-3 cells and the formation of bone metastases was studied in normal mice compared with mice that were rendered androgen-deficient by surgical castration, thus mimicking the situation in patients receiving antiandrogen therapy. Castrated mice had significantly elevated numbers of osteoclasts and developed significantly more bone metastases than intact control mice (Figure 5) [70]. This suggests that excessive bone resorption caused by androgen ablation may facilitate metastasis of prostate cancer cells to the bone, which is consistent with current hypotheses of how tumor cells colonize the bone. More importantly, daily treatment of both normal and castrated mice with zoledronic acid (1 μg/day) significantly reduced the incidence of bone metastases compared with untreated mice (Figure 5) [70]. This effect may be a result of reduced bone resorption and/or a direct antitumor effect. Zoledronic acid is currently being investigated in patients with early-stage prostate cancer to determine if it will reduce the incidence of bone metastases.

Mechanisms of antitumor effects

A variety of mechanisms have been proposed to explain the observed antitumor effects of zoledronic acid and other bisphosphonates. The existing evidence from animal models suggests that inhibition of tumor-induced osteolysis may be an important antitumor mechanism; however, there is also abundant in vitro evidence that bisphosphonates inhibit tumor cell proliferation, induce tumor cell apoptosis,

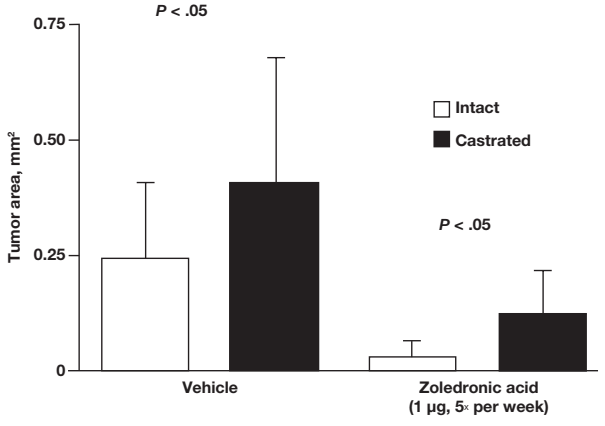

Figure 5. Growth of PC-3 bone metastases in intact or castrated male rats treated with either saline or zoledronic acid (1 μg/mouse/day) and injected intracardially with PC-3 cells. Data from Padalecki et al. [70].

antagonize tumor cell metastasis, and exert antiangiogenic effects. Any or all of these mechanisms may be involved, and the direct antitumor effects may help to explain how zoledronic acid can inhibit growth of visceral metastases.

It has been suggested that bisphosphonates may inhibit tumor growth in the bone and the ability of tumor cells to colonize the bone by reducing the numbers and activity of osteoclasts, thus reducing the release of bone-derived growth factors and making the bone less fertile "soil" [71]. This is consistent with evidence from animal models suggesting that by inhibiting osteoclastogenesis and osteoclast-mediated bone resorption it is possible to profoundly inhibit the formation of bone metastases [70,72,73]. However, this may not be the whole story.

Bisphosphonates also clearly have direct antitumor activity in preclinical studies. One of the primary mechanisms by which bisphosphonates exert direct antitumor effects is via induction of caspase-dependent apoptosis [43,45–47,49,50,74]. Bisphosphonates have also been shown to directly inhibit adhesion of tumor cells to extracellular matrix proteins and the ability of tumor cells to migrate through a synthetic medium that mimics the extracellular matrix [53–56,75]. Zoledronic acid has been shown to dose-dependently inhibit adhesion of MCF-7 and MDA-MB-231 breast cancer cells to a variety of extracellular matrix proteins [53–56,75]. In addition, several nitrogen-containing bisphosphonates, including zoledronic acid, ibandronate, and risedronate, have been shown to inhibit the ability of human breast and prostate cancer cells to invade Matrigel™ at subnanomolar concentrations [53]. The mechanism responsible for this effect does not appear to be apoptosis; even at micromolar concentrations (10^{-6} M) zoledronic acid did not induce apoptosis. Similar findings have also been reported for alendronate, and this effect was reversed by adding geranyl geraniol and trans-trans-farnesol [76]. By this mechanism, bisphosphonates may limit the metastatic potential of tumor cells.

Finally, both in vitro and in vivo studies have demonstrated that zoledronic acid has antiangiogenic activity. In vitro, zoledronic acid has been shown to dose-dependently inhibit the proliferation of human umbilical vein endothelial cells (HUVEC) in response to basic fibroblast growth factor (bFGF) [57], and it inhibited capillary-like tubule formation by HUVEC in the Matrigel assay [58]. Low doses of zoledronic acid have also been shown to inhibit soft-tissue angiogenesis in a growth factor implant model (Figure 6) [57]. At doses of 1, 10, or 100 μg/kg/day × 5 days by SC injection, zoledronic acid dose-dependently reduced blood content and wet weight

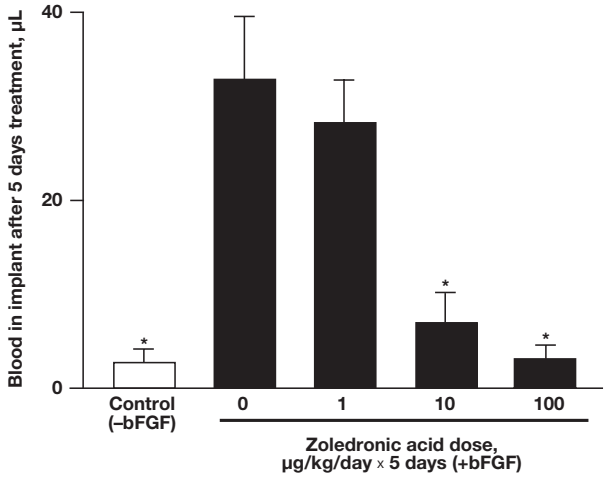

Figure 6. Blood volume in tissue chamber implants impregnated with basic fibroblast growth factor (bFGF) in mice treated with zoledronic acid 1, 10, or 100 µg/kg/day × 5 days. *Indicates statistically significant reductions compared with controls not treated with bFGF ($P < 0.01$). Adapted with permission from Wood et al. [57].

of newly formed tissue around semi-permeable chambers containing bFGF. In another animal model, zoledronic acid was shown to decrease revascularization (as measured by vessel area) of the ventral prostate gland in castrated rats treated with testosterone [58]. The observed inhibitory effects of zoledronic acid on endothelial cell proliferation, adhesion, and migration appear to be mediated, at least in part, by modulation of the expression of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins and the 67-kD laminin receptor [77,78]. Another potential mechanism is modulation of proangiogenic growth factors, including vascular endothelial growth factor and bFGF [79].

Conclusions and future directions

The clinical role of bisphosphonates in the treatment of prostate cancer continues to evolve. Zoledronic acid, in particular, appears to have great potential for maintaining bone health in patients with prostate cancer. In men with early stage disease, zoledronic acid prevents bone loss associated with ADT and improves BMD, which can be expected to reduce the risk of fractures and of bone metastasis. Zoledronic acid is also the only bisphosphonate proven effective for the prevention of skeletal complications in patients with advanced prostate cancer. In patients with bone metastases, treatment with 4 mg zoledronic acid (every 3 to 4 weeks for up to 2 years) significantly reduced the incidence and risk of skeletal complications and provided long-term, statistically significant reductions in bone pain compared with placebo [28].

Preclinical evidence has demonstrated that zoledronic acid has antitumor activity against prostate cancer cell lines and bone metastases in animal models of human prostate cancer, and a variety of potential mechanisms to explain these effects have been demonstrated. There is also clinical evidence in patients with breast cancer that bisphosphonates can prevent bone metastasis, and in patients with renal cell carcinoma, zoledronic acid delayed tumor progression in bone. Based on the available preclinical and clinical evidence that zoledronic acid may have beneficial effects on tumor development and progression in bone, zoledronic acid is being investigated for the prevention of bone metastasis in patients with early stage prostate cancer. Studies are ongoing to further define the clinical benefit of zoledronic acid in patients with prostate cancer throughout the course of their disease.

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