Targeting Factors Involved in Bone Remodeling as Treatment Strategies in Prostate Cancer Bone Metastasis

Robert L. Vessella and Eva Corey

Abstract

Prostate cancer is the most commonly diagnosed cancer in men within the western world and the third leading cause of cancer-related deaths. Even if the cancer is considered localized to the prostate, there is a 15% to 20% incidence of subsequent metastatic disease. Prostate cancer has a very high proclivity for metastasizing to bone, with ~90% of men with advanced disease having skeletal lesions. The prostate cancer metastases are characteristically osteoblastic, with extensive new bone deposition, unlike other tumors that metastasize to bone and cause an osteolytic response reflective of bone degradation. There are a considerable number of studies relating to inhibition of the osteoblastic response, including interference with endothelin-1, bone morphogenetic proteins, and Wnt signaling pathways. Within the past few years, several studies showed that increased osteolytic activity also occurs in the background of the prostate cancer skeletal metastases. Because growth factors are being released from the bone matrix during degradation, it suggests that inhibition of osteolysis might be effective in slowing tumor growth. Several strategies are being developed and applied to affect directly the osteolytic events, including use of bisphosphonates and targeting the critical biological regulators of osteoclastogenesis, receptor activator of nuclear factor-κB and receptor activator of nuclear factor-κB ligand. This review focuses on several of the clinical and preclinical strategies to inhibit the growth of prostate cancer cells in bone and to alleviate the multitude of associated skeletal-related events.

Prostate cancer is the most common malignancy of men and is expected to be newly diagnosed in >200,000 men in 2005. Truly localized disease can be treated successfully by surgery, radiation, or a variety of other methods. However, even when the disease is thought to be localized to the prostate, approximately 15% to 20% of these patients later return with metastatic disease, and there are also several patients who initially present with known disease outside the prostate. For these men, the traditional first line of treatment is androgen ablation, a strategy that takes advantage of the tumor’s dependence on androgens as a growth factor. Yet, during a period of months to years, prostate cancer cells adapt to an androgen-depleted environment and progress from androgen dependence to hormone refractory in a process that is still poorly understood. Treatment of hormone-refractory disease has been largely unsuccessful in prolonging survival, although treatment with the taxanes has shown some significant promise in recent studies.

The hallmarks of advanced prostate cancer are its high proclivity to metastasize to bone and the consequential osteoblastic response. In our survey of 153 bone specimens, acquired through our rapid autopsy program from 14 patients who had died of advanced prostate cancer, we found that 100% of the patients had at least microscopic evidence of bone metastases. Another finding of interest was the high percentage of patients (~70%) who had predominantly skeletal metastases with insignificant (<10 cm³, total) nonbone metastases. In this group of patients, small specks of metastases were frequently noted in the visceral organs, but it appeared as if these metastatic foci were not able to flourish and grow.

Prostate cancer cells in the bone environment express several factors associated with bone remodeling, a process called osteomimicry (3). These numerous factors include the bone morphogenetic proteins (BMP), transforming growth factor-β, parathyroid hormone-related protein, endothelin-1, adrenomedullin, osteoprotegerin (OPG), receptor activator of nuclear factor-κB (RANK), and RANK ligand (RANKL). The diversity of these factors is remarkable, and the extent of effects on normal bone remodeling is extremely complex. Clearly, some are closely linked to the osteoblastic response, whereas others are primarily linked to osteoclastogenesis. Perhaps due to the complexity and diversity of factors produced by the prostate cancer cells, the histologic and phenotypic heterogeneity of bone metastases in a given patient is dramatic (2, 4).

One unique aspect of prostate cancer that distinguishes it from other malignancies is the expression of prostate-specific antigen (PSA). PSA is a serine protease that has been used as a marker for the early detection of prostate cancer and for monitoring its response to therapy (5, 6). Many investigators have speculated that PSA may perturb the remodeling processes.

Authors’ Affiliations: 1Department of Urology, University of Washington Medical Center and Puget Sound Veterans Administration Health Care System and 2Department of Urology, University of Washington Medical Center, Seattle, Washington

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Requests for reprints: Robert L. Vessella, Department of Urology, Box 356510, University of Washington Medical Center, 1595 Northeast Pacific Street, Seattle, WA 98195. E-mail: vessella@u.washington.edu.

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to favor an osteoblastic response (7–9). Other prostate-associated serine proteases, such as hK2 and hK4, also have catalytic properties that theoretically could activate or deactivate critical factors involved in bone remodeling.

Despite the fact that the overall characteristic response associated with prostate cancer bone metastasis is osteoblastic, there is now ample evidence that osteolytic events are also ongoing. Histomorphometric studies from our group clearly document areas of eroded surfaces, and markers of osteolysis are frequently elevated in patients with advanced disease (2, 10–13). Some of the osteolysis may be attributed to androgen deprivation, whereas osteolytic factors expressed by the prostate cancer cells may also play a role (14, 15). Regardless of the initiating events, osteolysis is highly likely to result in the release of potent growth factors from the bone matrix that favorably affect the growth of the cancer cells. To address this aspect directly, several studies have evaluated the effects of osteolysis-inhibiting agents on prostate cancer bone metastases, including targeting the mature osteoclast through the use of bisphosphonates or the differentiation of preosteoclasts by exploiting features of the OPG/RANK/RANKL system.

Herein, we concisely review some of the treatment strategies being implemented at the preclinical level and in clinical trials that target the factors or processes thought to be important in prostate cancer bone metastases. Specifically, we address attempts to minimize and/or reverse the predominant osteoblastic response and to inhibit the osteolytic events that seem to contribute appreciably to the overall pathophysiology. These targeted therapies are not cytotoxic but are considered cytostatic with the goal of slowing tumor progression and/or inhibiting the events that lead to high morbidity (16). Success with these interventions could turn hormone-refractory prostate cancer metastatic to bone into a clinically manageable chronic disease.

Strategies to Minimize or Reverse the Osteoblastic Response

**Background.** The classic osteoblastic lesions of prostate cancer bone metastasis are evident by radiography and histologic analysis. It is characterized by deposition of new woven bone by osteoblasts in a chaotic, unorganized fashion, interlaced between foci of tumor cells. Elevated serum levels of bone-specific alkaline phosphatase, a marker of osteoblast proliferation, are often noted (11). At least 12 factors that regulate osteoblast differentiation and proliferation are expressed by prostate cancer cells (reviewed in refs. 17, 18). Although space does not allow a discussion of each of these, a few for which preclinical or clinical efforts are ongoing will be highlighted.

**Preclinical and clinical efforts.** The BMPs are osteoinductive morphogens that are members of the transforming growth factor-β superfamily and critical for skeletal development (19, 20). Therefore, the fact that prostate cancer cells produce BMPs has led to the hypothesis that these factors may play a major role in the osteoblastic response. Furthermore, in an autocrine fashion, prostate cancer cells have receptors for the BMPs, which on binding to the ligand promote SMAD1 signaling and overexpression of OPG (an inhibitor of osteoclastogenesis; ref. 21). Along a similar line of investigation, recent studies show that BMP-2 and BMP-6 stimulate the invasive capability of prostate cancer cells (22). Therefore, inhibition of the BMPs may have clinical relevance. Noggin is a regulator of BMP activity and has been shown to inhibit the effects of BMP-6 in vitro on prostate cancer cells (23). In vivo, noggin-overexpressing prostate cancer cells had diminished growth in an intratibial model (24). In a comparable study, anti-BMP-6 antibodies reduced the LuCaP 23.1 prostate cancer xenograft-induced osteoblastic activity (22). These recent efforts support the hypothesis that inhibition of the BMPs may have clinical value in the management of prostate cancer bone metastases.

The Wnts are a large family of proteins that are involved in bone formation. Wnts are also produced by prostate cancer cells. Acting through two interacting receptors, frizzled and LRP5/6, the canonical Wnt signaling pathway results in stabilized cytoplasmic β-catenin, which then translocates to the nucleus to regulate as yet defined bone formation genes (25). Wnt activity is inhibited by regulatory proteins, such as dickkopf-1 (26). In a set of recent preclinical studies, Hall et al. (27) showed the importance of Wnt signaling in inducing osteogenesis. They showed that inhibition of dickkopf-1 by transfection of short hairpin RNA turned the normally highly osteolytic PC-3 cell line into an osteoblastic line. In contrast, overexpression of dickkopf-1 in the C4-2B cell line, which yields a mixed osteolytic-osteoblastic lesion in intratibial models, resulted in the cells producing a highly osteoblastic lesion. This is the first direct in vivo evidence of the involvement of the Wnt signaling pathway in prostate cancer bone metastasis. Certainly, novel inhibitors of Wnt signaling will be used in preclinical prostate cancer models in the near future.

A newly discovered factor, soluble ErbB3, has been shown to have osteostabilizing activity (28, 29). Soluble ErbB3 was isolated and identified from bone marrow supernatants obtained from patients with prostate cancer bone metastases. Thus far, this investigative group is the only one to associate this factor with the osteoblastic response, and in as yet unpublished but presented work, it stimulated bone formation in preclinical studies.

The first clinical trial to specifically target osteoblasts in patients with metastatic prostate cancer was based on evidence that endothelin-1, a powerful vasoconstrictor, was also a significant factor in stimulating osteoblasts (30, 31). Furthermore, endothelin-1 plasma levels were elevated in patients with prostate cancer, and there was substantial documentation that endothelin-1 was expressed by prostate cancer cells (32). In preclinical models, administration of an antagonist (ABT-627) to the endothelin-A receptor significantly reduced the osteoblastic response induced by endothelin-1-producing amnion and breast cancer xenografts and reduced the number of metastatic lesions (33, 34). Several in vitro and preclinical studies have validated the potentially critical role of the endothelin axis in the tumor-induced osteoblastic response (35, 36). In a recent review, Smith and Nelson (37) listed the 13 clinical trials that have been completed or are ongoing with atrasentan (trade name for ABT-627). Overall, atrasentan appears to be well tolerated and delays progression of hormone-refractory prostate cancer in some men (38–40). Consistent with the dual activity observed in the preclinical investigations, there was also a significant attenuation in blood levels of PSA and the bone formation markers total alkaline phosphatase and bone alkaline phosphatase, implying both tumor cells and osteoblasts were affected (41). One phase III clinical trial has been completed (M00-211) and the other is...
ongoing (M00-244). The recently completed M00-211 trial was designed to evaluate the role of atrasentan in men with hormone-refractory disease who had radiographic evidence of metastatic disease. The treatment failed to achieve significance in the primary and most secondary end points. The median difference between the two arms of the M00-211 trial was only 7 days based on the Kaplan-Meier curve at the first scan (3 months) when the two curves were close. However, when the data were reanalyzed using the hazard ratio test, the atrasentan arm was 0.813 (95% confidence interval, 0.685-0.965; \( P < 0.016 \)).

Using this method, one would interpret the data as meaning that men with bone metastases receiving atrasentan had a 19% delay in time to disease progression. Thus, more clinical investigations remain to be done before the exact clinical benefit of atrasentan for men with hormone-refractory metastases can be determined.

### Strategies to Minimize or Reverse the Osteolytic Component

#### Background

The osteolytic component of prostate cancer bone metastases has only recently become fully appreciated. Several investigators have observed the presence of increased biochemical markers reflective of bone resorption in men with prostate cancer, and oftentimes the levels were higher than in predominantly osteolytic bone metastases, such as breast cancer (42–47). These markers include primarily the N-telopeptide of type 1 collagen and secondarily pyridinoline-cross-linked peptides and deoxypyridinoline-cross-linked peptides. The data are mixed as to how well these markers compared with PSA in detecting osseous metastases and in monitoring regression and progression (45, 46). Recently, Brown et al. (42) reported on correlation between bone marker levels and clinical outcome in prostate cancer patients, finding a significantly higher risk of (a) time to first skeletal-related event, (b) disease progression, and (c) death in prostate cancer patients with high N-telopeptide levels (\( > 100 \) nmol/mmol creatine). Others have subsequently shown that elevated N-telopeptide levels directly correlated with a higher risk of skeletal-related events (43).

Generally, men with prostate cancer bone metastases suffer from three osteolytic insults that result in decreased bone mineral density. In older men, there is a natural decline in hormone levels that are important in maintaining a balanced bone remodeling system (48, 49). Although the process is more gradual than encountered by menopausal women, it is nonetheless clinically apparent. Androgen deprivation therapy induces additional bone loss in prostate cancer patients that can exceed that in early-stage menopausal women (50–52). The third onslaught comes from factors produced by the prostate cancer cells within the bone environment that directly or indirectly promote osteoclastogenesis (e.g., interleukin-1, interleukin-6, interleukin-11, parathyroid hormone-related protein, and RANKL; refs. 14, 53). In addition to the morbidity associated with these osteolytic events, the degradation of bone releases a plethora of growth factors stored in the bone matrix, many of which are known experimentally to stimulate prostate cancer cell growth (e.g., transforming growth factor-\( \beta \); ref. 54).

These then become factors in the well-described “vicious cycle” that is a consequence of tumor metastases to bone (55). Accordingly, two complementary approaches have been applied in vivo to decrease these osteolytic events. The first and most studied uses bisphosphonates to directly impede the osteoclastic degradation of bone. A more recent approach uses current knowledge of osteoclastogenesis and inhibition of the OPG/RANK/RANKL regulatory system.

#### Preclinical and clinical efforts

**Bisphosphonates.** Bisphosphonates are pyrophosphate analogues that have high affinity for hydroxyapatite. They are thought to directly affect osteoclasts through a variety of mechanisms (56). In addition, there is mounting experimental evidence that the bisphosphonates result in antitumor effects (57–60) and that zoledronic acid, the newest generation of bisphosphonates, exerts anti–prostate cancer effects (61, 62).

In one of our recent investigations, we explored the effect of zoledronic acid on the prostate cancer xenografts PC-3 (osteolytic) and LuCaP 23.1 (osteoblastic) established in the tibia of severe combined immunodeficiency mice (63). The results from these studies showed that zoledronic acid significantly inhibited the growth of these tumors whether the administration scheme was designed as preventative or as treatment after establishment of tumor growth. It was especially noteworthy that the bisphosphonate had such a significant effect on the osteoblastic tumors. As partial confirmation of these findings, it was shown simultaneously that zoledronic acid and pamidronate induced apoptosis via inhibition of the mevalonate pathway in three prostate cancer cell lines (62). Of course, it was not evident from the in vivo studies whether zoledronic acid affected the prostate cancer cells due to direct effects on the xenograft (as shown previously in vitro), indirect effects through perhaps a reduction in release of growth factors from inhibitory action on the osteoclasts, or a combination of the two potential mechanisms. To address this issue, we compared subsequently the effects of zoledronic acid with Fc-OPG (see further discussion to follow; ref. 64). Fc-OPG has not shown any significant direct antitumor effects in vitro and in vivo, although it inhibits osteolysis. The data from this preclinical study strongly suggested that the effect of zoledronic acid or Fc-OPG on prostate cancer cells growing in bone was attributed to indirect effects probably related to inhibition of osteolysis. Another indirect mechanism of zoledronic acid, inhibition of angiogenesis, was not evaluated in these studies but may have been involved as others have noted (65–68).

Several recent reviews have summarized the use of bisphosphonates in clinical trials involving prostate cancer patients (16, 37, 69–72). Several randomized controlled trials of bisphosphonates for metastatic hormone-refractory prostate cancer have been completed: the Zometa 039 trial (73), two multicenter trials (032/INT 05) using pamidronate (74), and the National Cancer Institute of Canada Pr06 mitoxantrone and prednisone and clodronate trial (75). Of these, only the Zometa 039 study showed significant promise, showing a reduction in skeletal-related events, including bone pain and a trend (\( P = 0.09 \)) toward increased survival. The other studies failed to show significant benefits. This could be attributed to the lower potency of the other bisphosphonates compared with zoledronic acid, inadequate sample size, end point definition, and/or the advanced disease state of the patients accrued.
Overall, the unequivocal benefits of the bisphosphonates in attenuating loss of bone mineral density in postmenopausal women and aging men prompts continued optimism that they will have a significant role in the treatment of prostate cancer. In addition to the Zometa 039 trial of patients with advanced disease, there are ongoing studies to determine if zoledronic acid affects the course of disease in patients with early-stage prostate cancer. Finally, combinational therapies that target the bone microenvironment and those combinational therapies that target both the bone microenvironment and the tumor cells are under active study in preclinical prostate cancer models and in patients (76–79).

Fc-OPG. OPG is a critical regulator of osteoclastogenesis, serving as a soluble decoy receptor for RANKL and thereby inhibiting stimulation of osteoclast differentiation through the RANK/RANKL interaction. Accordingly, it has been theorized that a stabilized construct of OPG (OPG attached to the Fc immunoglobulin fragment) could be a treatment option for osteolytic diseases, including malignancies that have an osteolytic component. However, it has also been reported that OPG is a survival factor for prostate cancer cells by binding the apoptosis-inducer tumor necrosis factor–related apoptosis-inducing ligand (80–82).

At least five articles have shown the efficacy of OPG treatment on prostate cancer establishment in bone and/or growth using preclinical models (64, 81, 83–85). In four of these studies, investigators used Fc-OPG (64, 83–85). The fifth report used transfected C4-2 prostate cancer cells to overexpress OPG (81). It was shown repeatedly that OPG had an effect on the prostate cancer cells growing in bone rather than on those growing s.c. These data have been interpreted as showing that OPG affects prostate cancer growth in bone in an indirect manner by reducing osteolysis through suppression of recruitment and activity of osteoclasts.

**Soluble RANK-Fc and monoclonal antibodies to RANKL.** We mentioned previously that one of the potential drawbacks of using OPG as an interventional strategy for prostate cancer bone metastases is that OPG binds to tumor necrosis factor–related apoptosis-inducing ligand (80–82). Accordingly, two alternative approaches for blocking the RANK-RANKL interaction are the use of soluble RANK-Fc and monoclonal antibodies to RANKL (86, 87). In the first application of soluble RANK-Fc in a preclinical prostate cancer model, Zhang et al. (88) showed a reduction in tumor-induced osteoblastic lesions, a reduction in systemic bone remodeling markers, and a decrease in serum PSA. Similar to studies with Fc-OPG, there was no effect on s.c. implanted prostate cancer. Thus far, this is the only report on the use of soluble RANK-Fc in a model of prostate cancer bone metastasis. AMG-162 is a human monoclonal antibody that binds and neutralizes human RANKL. A single dose of AMG-162 in postmenopausal women resulted in a significant (>80%) and sustained (>6 months) decline in urinary type I collagen-cross-linked N-telopeptide, a marker of osteolysis (87). As yet unpublished work is ongoing in clinical studies on the effectiveness of AMG-162 in breast and prostate cancer bone metastasis.

**Conclusions**

The importance of the bone microenvironment to the pathophysiology and morbidity associated with prostate cancer bone metastasis is becoming increasingly apparent (89). The future direction in treating prostate cancer bone metastasis will not only involve the further enhancement of the targeted therapies described herein but will also most likely include combinations of these strategies. Furthermore, the targeting of factors in the bone microenvironment will be combined with therapies directed at the prostate cancer cells, such as docetaxel. This multipronged approach is already undergoing considerable study in preclinical models and early clinical investigations. During the next several years, there is the potential of turning treatment refractory prostate cancer bone metastases into a clinically manageable disease.

**Open Discussion**

**Dr. Guise:** Did you test the Fc-OPG in the LuCaP 23.1 model?

**Dr. Vessella:** Yes, we tested Fc-OPG in LuCaP 23.1 and observed decreased proliferation of tumor cells and decreased serum PSA levels.

**Dr. Guise:** I asked because the C4-2 is a little osteolytic. It’s a mixed osteolytic-osteoblastic, and a LuCaP appears to be really osteoblastic. We know that LuCaP 23.1 makes endocle, and I wonder if it may have some role in osteoblastic response.

**Dr. Clohisy:** In the tibia of the mouse, there is only a limited area where a tumor can grow because there is no lamellar bone base. The question is whether the effect on tumor volume is because of the size of the tumor or because there is a fixed space where it can grow.

**Dr. Vessella:** We believe that it is due to tumor volume. However, some of the tumors that are more advanced break out of the bone and grow, but in general, they are confined within the bone area.

**Dr. Clohisy:** Have you looked at whether the tumor is alive or whether it’s necrotic?

**Dr. Vessella:** It’s alive and growing. We don’t let the tumor grow to a point where it is inhibiting the well-being of the mouse, and so these are still viable growing tumors.

**Dr. Rogers:** Do you think it’s unlikely that there is a direct effect on the bisphosphonates because when you implant PC3 or C4-2s there is no effect on tumor growth subcutaneously? Do you think that could simply be because there is very little bisphosphonate either circulating or in soft tissue?

**Dr. Vessella:** That is certainly a possibility. I probably shouldn’t be so adamant that there is no direct effect because you are absolutely right. It could be that it is not localizing at the s.c. site as much as it is localizing at the bone site, which would be expected.

**Dr. Roodman:** In your warm autopsy series, do you have any patients who have died of other causes besides prostate cancer and were early in their disease so that you could look at what the early events are in their bones?

**Dr. Vessella:** We’ve had a few patients who’ve died by accident. For example, one patient tripped and hit his head and died from head trauma. Most of the patients in our rapid autopsy program have been fairly advanced, and unfortunately we have not conceived of a way to get early disease biopsies in these patients.

**Dr. Roodman:** Has anyone been able to look at bone formation markers in patients who are at high risk of bone
metastases in a prospective fashion to look at absorption versus formation as the major event?

Dr. Vessella: We don’t see any abnormally elevated bone-related markers in very early recurrent disease. Once you get into the more bulky bone disease, then these markers become prevalent, but we haven’t seen anything that could be used as a prognostic indicator at this point.

Dr. Weilbaecher: Your data suggest a huge heterogeneity and that even within the same tumor there is differential PSA production. This makes me rethink how we treat cancer and how we view response. Should we change how we treat metastatic cancer?

Dr. Smith: The standard of care is to continue androgen deprivation therapy life long, which is based on old literature where men with orchietomies and metastatic prostate cancer were progressively given testosterone with disastrous results. These are old data with a few patients, but that sort of experience precluded anyone from doing these experiments in metastatic disease at least. However, the current thinking is more toward the side that androgen receptor signaling is intact even in hormone-refractory disease. I was struck by what you said about some sites experiencing lost androgen receptor.

Dr. Vessella: Yes, in some of the bone metastasis sites, there can be complete loss of the androgen receptor but overall the androgen receptor is not only expressed but overexpressed. It is critical to realize that such heterogeneity does exist.

Dr. Smith: That’s new and interesting information.

Dr. Vessella: Another interesting finding is that all of these patients in our rapid autopsy program were androgen deprived and hormone refractory. We’ve taken over 100 tumor pieces from these patients and implanted them into immune compromised mice, which has led to 20 established xenograft lines, such as LuCaP 23.1. The majority of these lines, 90% or so, regrow as androgen-dependent xenografts. This shows that once you re-expose an androgen refractory tumor to the presence of androgen, it then becomes androgen dependent. If you now take this tumor and ablate androgens, it goes through the progression processes to again become androgen independent.

Dr. Lipton: Do you have any feeling for the heterogeneous relation of bulk disease? If you take small amounts of metastases, are they more constant versus bulk disease? Is it just a loss due to growth and hypoxia?

Dr. Vessella: In some of these bone metast, it is small disease and it could be marker positive or marker negative. It doesn’t seem to make a lot of difference on the extent of the disease.

Dr. Suva: Is it androgen dependency or androgen receptor dependency?

Dr. Vessella: There is no question that, in some situations, the androgen receptor is promiscuous and will respond to other stimuli other than androgen itself, but this is not always the case. You still have situations where in some cells the androgen receptor is not promiscuous. This is a whole field of investigation: how the cells go from being androgen dependent, probably being stimulated just by androgens upfront, to then being depressed by the removal of androgens, and then almost universally beginning to regrow in the absence of androgens. This subsequent growth response is probably due to some kind of receptor stimulation due to other types of hormones or mechanisms. Another possibility is that androgen levels at the tumor site are not completely ablated and perhaps, even the presence of very low androgen levels might be sufficient to sustain tumor growth.

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