Targeting Bone Physiology for the Treatment of Metastatic Prostate Cancer

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Abstract: Metastatic prostate cancer has a unique predilection for bone that can lead to significant clinical sequelae, such as fracture and cord compression. This tropism for bone yields not only clinical challenges, but also opportunities to understand the tumor biology in bone and to develop relevant therapeutic strategies. The process by which tumor cells migrate to bone, remain dormant, and then colonize and expand is based on complex interactions between prostate cancer tumor cells and the host microenvironment. This review will provide an overview of these interactions as well as therapies targeting osseous metastases in castration-resistant prostate cancer.

Introduction

Bone is a common site for metastatic expansion for many solid tumors, but it is singularly characteristic of prostate cancer: 80–90% of men with advanced prostate cancer manifest disease in bone.[1,2] Skeletal metastases impair quality of life by causing morbidity, pain, pathologic fracture, and spinal cord compression. To date, bone-directed therapies that have been approved by the United States Food and Drug Administration (FDA) can palliate bone pain or prevent skeletal complications, but they have not been shown to prolong life. These therapeutic aims need not be mutually exclusive, however, and targeting tumor in bone as well as the stroma that supports malignant tumor cells has the potential to achieve several complementary treatment goals.

This review will focus on the tumor biology of bone and the bone microenvironment. Understanding the mechanisms underlying the development of skeletal metastases in prostate cancer provides a framework for the discussion of existing and novel treatments.

Pathophysiology

Overview of Tumorigenesis in Bone

Skeletal metastases develop in a vicious cycle, with the tumor cell manipulating and recruiting resident host cells, and resident cells

further supporting cancerous growth.[3,4] The scientific origins of this cycle date back to 1889 with Stephen Paget's seed and soil hypothesis, which postulated that a malignant cell (the seed) requires a fertile soil (a favorable microenvironment) to grow.[5] Indeed, more contemporary research has elucidated the cross-talk between seed and soil that is vital to cancerous growth.[6-8] This dialogue between cells involves an exchange between growth factors—such as transforming growth factor β (TGFβ), insulin-like growth factor (IGF), and platelet-derived growth factor (PDGF)—and bone morphogenic proteins (BMPs), cytokines, and cell adhesion molecules.[6,9] While bone marrow endothelial cells, hematopoietic stem cells, and other local cells such as fibroblasts participate in this dialogue, perhaps the best studied and most highly implicated interactions in bone metastases occur between the osteoclast, osteoblast, and tumor cell.

Bone is in a constant state of remodeling, typified by osteoclast-mediated bone resorption and osteoblast-mediated bone formation. Dysregulation in this balance is common to many bone disorders, such as osteoporosis, and underlies the development of solid tumor bone metastases. Prostate cancer metastatic to bone is generally thought of as an osteoblastic process, though there is abnormal osteoclastic activity as well.[3,10,11] Osteoclasts are myeloid-derived cells that are able to adhere to the surface of bone via αvβ3 integrin. This integrin is upregulated in prostate adenocarcinoma but not in normal prostate tissue.[12,13] Once adherent to the surface of bone, osteoclasts demineralize the bone matrix and destroy matricellular proteins.[14-16] They do so by creating a resorption pit on the surface of bone and secreting enzymes that signal degradation of underlying bone, the products of which may be internalized by the osteoclast or released into the microenvironment. This process is counterbalanced by osteoblasts—cells derived from mesenchymal stem cells—which synthesize bone matrix collagenase and rebuild bone. This harmony is dysregulated in skeletal metastases and begins before tumor cells proliferate in bone.

Tumor Cell Homing to Bone

The manner in which prostate cancer can metastasize to the bone has been described as a 4-stage process of homing to bone, dormancy, colonization, and expansion (Figure 1).[6,17] Prostate cancer's affinity for bone is a reflection, in part, of bone's potential to attract tumor cells and provide a hospitable microenvironment. Calcium is released during resorption of bone, and ionized calcium is thought to stimulate proliferation as well as encourage homing of tumor cells to the area,[18,19] specifically tumor cells known to express a calcium-sensing receptor.[20]

The initial attraction, or homing, of prostate cancer tumor cells to bone is largely regulated by a series of integrins and chemokines produced by the bone marrow stromal cells. A well-studied interaction involves the G protein-coupled receptor CXCR4, which is on the tumor cell, and its ligand, CXCL12, which is expressed by bone marrow stromal cells and osteoblasts.[21,22] CXCL12 promotes homing to bone as well as tumor progression, and represents an early event in the osteoblast contribution to bone metastases.[21-23] CXCL12/CXCR4 also attracts and retains hematopoietic stem cells in the bone marrow.[24] Indeed, CXCR4 inhibitors mobilize hematopoietic stem cells and have been used in hematologic malignancies for this purpose.[25,26] Treatment with the CXCR4 inhibitor AMD3100 in PC3 prostate cancer cell lines has been shown to decrease the prostate cancer progenitor populations (CD44+/CD133+) by 2.2-fold. In contrast, docetaxel-treated controls experienced a 2.1-fold increase in progenitor populations.[27]

Androgens can induce CXCR4 in prostate cancer cells expressing the TMPRSS2-ERG fusion protein, a common gene rearrangement in prostate cancer.[28,29] Activation of the CXCR4/CXCL12 pathway promotes nuclear translocation of wild-type and mutant androgen receptor in prostate cancer cell lines.[30] Hence, the androgen receptor may play a role in homing prostate cancer cells to bone as well as driving tumor growth. These relationships require further investigation in order to elucidate potential therapeutic targets, perhaps in earlier stages of disease.

Tumor Cell Dormancy

Once in the bone marrow, tumor cells may remain quiescent or colonize. Dissemination of these cells likely occurs early in the development of prostate cancer, although the majority of disseminated tumor cells (DTCs) remain dormant. Evidence of this dormancy is supported by the prevalence of DTCs at the time of prostatectomy in patients with radiographically-localized disease.[31,32] DTCs are typically sampled by bone marrow aspiration or biopsy from the iliac crest. In a study of 569 patients prior to radical prostatectomy, Morgan and colleagues found that 408 patients (72%) had evidence of DTCs.[31] They also studied an analytic cohort of 98 patients considered disease-free after prostatectomy who later underwent bone marrow aspiration, and found DTCs present in 56 patients (57%). Fourteen patients experienced biochemical recurrence after prostatectomy; DTCs were detected in 12 patients (86%).

In other series of untreated localized prostate cancer, however, the rates of DTC have been much lower—between 13% and 18%. The prognostic significance of DTC detection in the preoperative versus postoperative setting is uncertain.[33,34] Weckermann and colleagues observed comparable rates of cytokeratin-positive DTCs

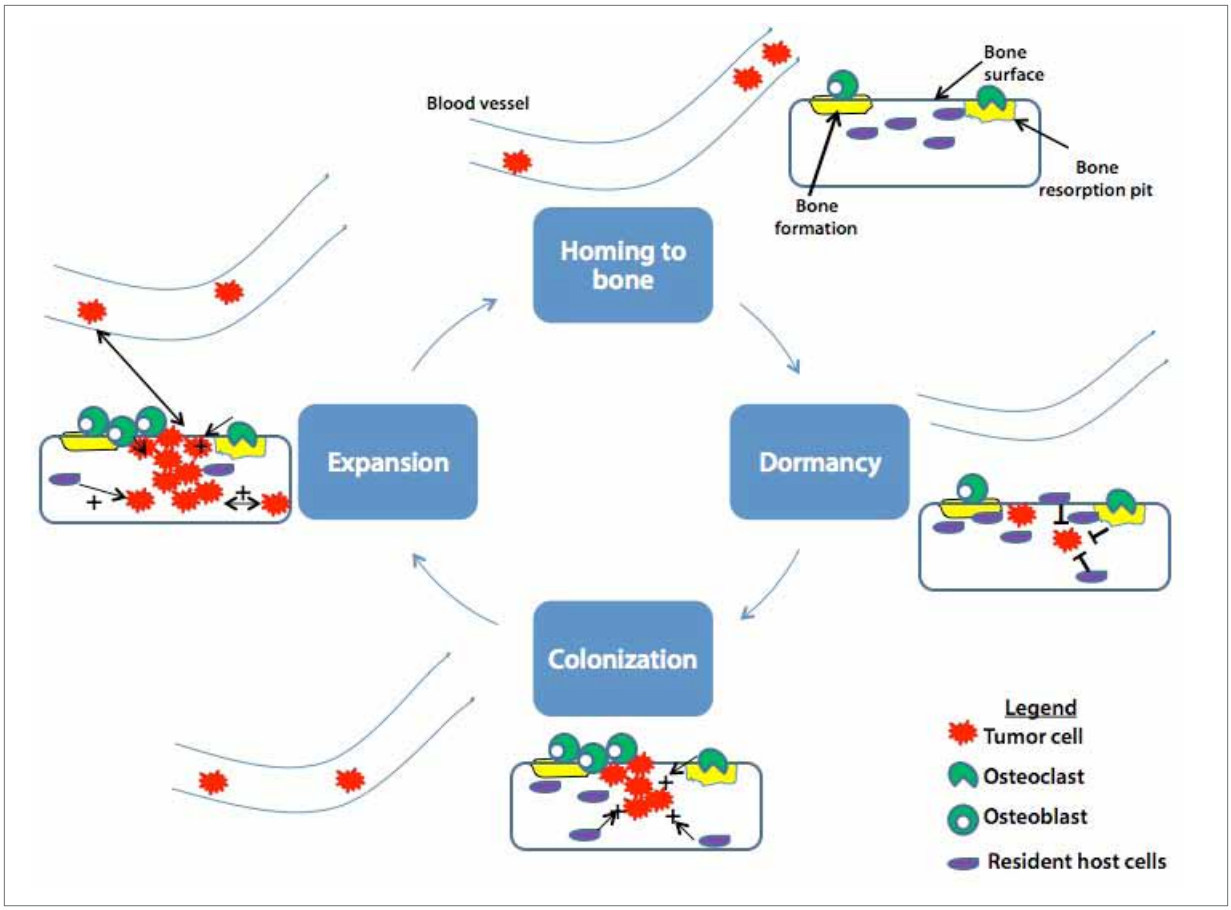

Figure 1. The process of metastatic growth of prostate cancer in bone. This simplified schema demonstrates the phases of bone metastatic growth from prostate tumor cells homing to bone, to a variable period of tumor cell dormancy or quiescence in bone, and then colonization and expansion in bone. This progression is characterized by complex interactions between osteoclasts, osteoblasts, and other resident bone cells (hematopoietic stem cells, lymphocytes, etc.) and prostate cancer tumor cells.

among preoperative and postoperative patients, but found that patients with cytokeratin-positive DTCs in the pretreatment bone marrow were at a 5.5-fold higher risk of developing metastatic disease within 48 months. However, the detection of DTCs 6 months to 10 years after surgery was not associated with poor clinical outcome.[33] In contrast to DTCs, circulating tumor cells (CTCs) obtained via peripheral blood are rarely detected in localized prostate cancer, even in patients with adverse pathology, such as extracapsular extension.[35,36]

Tumor Cell Colonization and Expansion

The ability of dormant prostate cancer cells to then proliferate, crowding the hematopoietic stem cell niche, relies on a complex series of autocrine, paracrine, and host microenvironment interactions. Tumor-derived endothelin-1 stimulates osteoblasts via the endothelin receptor type A, which leads to pathologic bone formation.[37,38] The osteoblast also expresses cadherin, a cell-cell adhesion molecule. Cadherin-11 is highly expressed in PC3 cell lines, as well as in human metastatic tissue. It promotes prostate cancer migration and invasion by adhering prostate cancer tumor cells to host osteoblasts.[39] Androgen depletion has been associated with cadherin-11 upregulation.[40] In specimens obtained during salvage prostatectomy in men receiving androgen deprivation therapy (ADT), 86% of patients (22 of 26 patients) showed increased cadherin-11 expression by immunohistochemistry. In contrast, 14% of specimens from primary prostatectomies in men not receiving ADT showed focal cadherin-11 expression. This raises the possibility that ADT may lead to increased osteoblast-derived cadherin-11, potentially promoting dissemination in bone. This is an active area of research, and therapeutic targets of cadherin-11 are in development.

The process of expansion in bone is also mediated by the production of matrix metalloproteinases (MMP), which degrade extracellular matrix proteins and are crucial to metastatic spread.[41-43] Tumor cells produce MMP, as do osteoclasts, and therapeutic targets are in development.[44-46] One mechanism that has implicated MMP in

skeletal metastases is its ability to activate receptor activator nuclear factor kappa B ligand (RANKL). RANKL, a tumor necrosis factor (TNF) family cytokine, is produced by the osteoblast, then binds to the RANK receptor on the osteoclast precursor, stimulating bone resorption. TGFβ, an autocrine protein and product of osteolysis, can also stimulate RANKL via the parathyroid hormone-related protein (PTHrP) pathway on tumor cells.[47] TGFβ is highly implicated in the vicious cycle associated with bone metastases.[6,48,49] Osteoblasts provide additional regulations in the RANKL pathway by secreting a soluble decoy, osteoprotegerin, which prevents RANKL from binding to its receptor. Despite these apparent balances, the normal coupling between osteoclast and osteoblast activity goes awry in metastatic disease, and the characteristic osteoblastic lesions are a result of zealous bone formation. In a cell model of castration-resistant prostate cancer (CRPC) exposed to soluble growth factors intended to promote metastasis, RANKL expression increased with metastasis formation.[50]

The role of androgens fueling prostate cancer, even in an androgen-deprived state, is well established.[51,52] However, it is noteworthy that androgens are intimately and specifically involved with the process of tumorigenesis in bone. As discussed previously, androgens can induce the integrins and cell adhesion molecules needed by tumor cells to home to and proliferate in bone; androgens also stimulate Wnt, a key pathway in osteoblast formation. Wnt-signaling molecules function via an autocrine mechanism to stimulate and promote survival in prostate cancer cells.[53,54] Evidence for this dialogue between the androgen receptor pathway and Wnt pathway comes from increased expression of runt-related transcription factor 2 (RUNX2), as well as the adherent junction protein β-catenin.[55-57] This cross-talk between the bone microenvironment and androgen pathways is bidirectional and complex. Unraveling such pathways, perhaps via a systems biology approach, may lead to more effective therapies.

Therapeutic Targets for Bone Metastases

Harnessing our understanding of the bone microenvironment, tumor cells, and supporting stroma can leverage therapeutic options. Despite our growing knowledge of such interactions, approved treatment options in metastatic CRPC (mCRPC) largely fall into the realm of tumor-directed agents using either chemotherapy or novel anti-androgen/receptor-directed therapy. The approved therapeutics that are designed to manipulate the bone microenvironment do so by impairing osteoclast activity (zoledronic acid and denosumab [Xgeva, Amgen]) or by delivering bone-seeking radiopharmaceuticals to sites of osteoblastic activity (strontium-89, samarium-153). A number of agents with the potential to specifically target skeletal metastases in CRPC are under investigation. Supported by preclinical data, these agents have been developed to interfere with the process of tumor cell expansion in bone; ongoing trials will determine if this translates into therapeutic benefit.

Impairing Osteoclast Resorption

Although prostate cancer bone metastases are classically osteoblastic lesions, it is clear that osteoclasts also play a pivotal role. As such, impairing the osteoclast's resorptive mechanisms are strategies with actionable targets. Bisphosphonates are derived from inorganic pyrophosphate and prevent osteoclastic activity by binding to hydroxyapatite, the mineral component of bone. These agents were believed to induce apoptosis in osteoclasts; however, more recent data from bone marrow biopsies of patients receiving bisphosphonates indicate that there may actually be increased osteoclastic activity over time.[58,59] This suggests a number of possibilities: that bisphosphonates may not truly induce apoptosis, that the effect is temporary, or that compensatory mechanisms are at play. Zoledronic acid, a third-generation bisphosphonate, is the only bisphosphonate approved by the FDA for the prevention/delay of skeletal-related events (SREs) in mCRPC. SREs include pathologic fracture, cord compression, the need for radiation therapy or surgery to bone, and worsening bone pain in some trials.

Zoledronic acid was the sole agent approved to prevent/delay SREs until denosumab was approved in November 2010. Denosumab first received approval for the prevention of SREs in solid tumors metastatic to bone based largely on the results of breast cancer trials.[60] Whether denosumab is appropriate for metastatic castration-sensitive prostate cancer is unknown, as published trials in the metastatic setting are restricted to castration-resistant disease. Zoledronic acid has been studied in a phase III trial for castration-sensitive disease and did not reduce the risk of SRE or death.[61] Table 1 summarizes the use of zoledronic acid and denosumab for the various clinical states defined in prostate cancer.

The question of whether denosumab, a fully humanized monoclonal RANKL inhibitor, is preferable to zoledronic acid must be viewed not only in the context of clinical trials but also patient factors. Table 2 reviews primary and secondary results of the phase III trials in mCRPC. Favorable qualities of denosumab include its subcutaneous administration, lack of renal toxicity, and fewer acute phase reactions. The randomized double-blind trial in mCRPC found that osteonecrosis of the jaw (ONJ) rates are similar (2% with deno-

Table 1. Approved Agents for SRE Prevention or Bone Fragility, by Clinical State

Clinical State	Approved Agent	RCT in This Clinical State to Support Approval
Localized	None	n/a
Localized, rising PSA, noncastrate	None	n/a
Castrate, nonmetastatic	Denosumab is approved for bone fragility in ADT but not for metastasis or SRE prevention	Denosumab vs placebo. % change BMD at 24 months: 5.6% vs -1%; *P*<.001, n=1,468[90] Denosumab vs placebo. Bone-metastasis-free survival: 29.5 months vs 25.2 months; HR, 0.85; 95% CI, 0.73–0.98; *P*=.028; n=1,433[63]
	Zoledronic acid is not approved for bone fragility in ADT, metastasis, or SRE prevention	ZEUS trial: zoledronic acid vs placebo will address nonmetastatic disease; endpoint is proportion of patients with 1 bone metastasis after 48 months; study ongoing[69]
Metastatic, castration-sensitive	Denosumab is approved in solid tumors metastatic to bone, although there are no published data in metastatic, castration-sensitive disease.	n/a
	Zoledronic acid is not approved for SRE prevention in castration-sensitive disease	NCT00079001 (CALGB 90202): Zoledronic acid vs placebo addressed castration-sensitive disease and did demonstrate a reduced risk of SRE or death[61]
Metastatic, castration-resistant	Zoledronic acid is approved for SRE prevention in mCRPC	Zoledronic acid vs placebo. % of patients with SRE at 15 months: 33.2% vs 44.2%; *P*=.021, n=64[91]
	Denosumab is approved for SRE prevention in mCRPC	Denosumab vs placebo. Time to first on-study SRE: 20.7 months vs 17.1 months; HR, 0.82; 95% CI, 0.71–0.95; *P*=.0002, n=1,904[62]

ADT=androgen deprivation therapy; BMD=bone mineral density; FDA=Food and Drug Administration; mCRPC=metastatic castration-resistant prostate cancer; RCT=randomized clinical trial; SRE=skeletal-related event.

sumab and 1% with zoledronic acid).[62] A known risk factor for ONJ is oral trauma (eg, dental extractions), and the chronicity and frequency of dosing are other risk factors. Another notable toxicity is hypocalcemia. In the large phase III trial in mCRPC, grade 3 hypocalcemia was 5% for patients treated with denosumab compared with 1% for patients treated with zoledronic acid. Of note, this was a population of patients who had never been exposed to prior bisphosphonates, and had been diagnosed with metastatic bone disease an average of 3.9–5.2 months before study entry (and thus were relatively early in their metastatic disease course). Hypocalcemia may be more problematic in patients with more advanced disease. The optimal timing and duration of therapy to prevent SREs must be balanced against the known toxicities of these agents.

The toxicity profiles of these agents must also be considered when evaluating their use in earlier disease states. Denosumab has been, and zoledronic acid is currently, under investigation for metastasis prevention, although the regulatory approval pathways are not established. A large phase III study of 1,432 patients with nonmetastatic CRPC has demonstrated a 3.7-month delay in time to first bone metastasis in patients at high risk for metastatic disease (rising PSA, a PSA doubling time <10 months, and/or PSA >8) who received subcutaneous denosumab 120 mg every 4 weeks versus placebo.[63] The delay in metastases did not translate into increased survival. While it may be conceptually appealing to postulate that RANKL inhibition can alter the microenvironment and delay metastases, it is less clear that this offers a significant clinical advantage. As some have noted,[64] the time delay to detectable metastatic disease is similar to the time delay to SREs in mCRPC—approximately 1 scanning interval—and there is no survival advantage. Indeed, the FDA rejected the proposal to approve denosumab for this indication.[65] Denosumab does come with side effects and has a non-negligible cost. The duration of bisphosphonate exposure is a known risk factor for ONJ,[66,67] and the same is suspected for denosumab. A recent meta-analysis of randomized trials using denosumab in solid tumors or myeloma found that the cumulative incidence of ONJ was 0.8% at 1–12 months, 1.8% at 24 months, and 1.8% at 36 months.[68] Hence, duration of exposure

Table 2. Positive Phase III Trials of Therapies That Prevent/Delay SREs in mCRPC by Targeting Osteoclast Activity

Study	Study Size	Treatment	Results
Zoledronic acid (Saad et al. 2002, 2004)[91,92]	N=643	Zoledronic acid 4 mg IV q3wk vs placebo	Primary endpoint at 15 months • ↓ Proportion of patients with SRE: 44.2% vs 33.2% (*P*=.021) Secondary/exploratory results from continuation cohort at 24 months • ↑ Median time to SRE: 488 vs 321 days (*P*=.009) → No survival benefit: 546 vs 464 days (*P*=.91)
Denosumab (Fizazi et al. 2011)[62]	N=1,904	Denosumab 120 mg SC q4wk vs zoledronic acid 4 mg IV q4wk	Primary endpoint at 12.2 months • ↑ Time to first on-study SRE: 20.7 vs 17.1 months (*P*=.0002 for noninferiority and *P*=.008 for superiority) Exploratory endpoints → No survival benefit: 19.4 vs 19.8 months (*P*=.65) • No PFS benefit: 8.4 vs 8.4 months (*P*=.30) • ↑ Change UNTx from baseline at week 13: 40.3% vs 28.4% (*P*<.001)

IV=intravenous; SC=subcutaneous; SREs=skeletal-related events; UNTx=urine N-telopeptide; wk=weeks.

may be a risk factor for ONJ with denosumab as well, although the cumulative risk may plateau. A logical concern is that with earlier use of these agents, such as in the nonmetastatic setting, there is a greater likelihood for chronicity of use and potentially a greater risk for ONJ. Whether this concern is merely theoretical requires continued prospective evaluation. Zoledronic acid is also under investigation in the large randomized trial ZEUS (Zometa European Study), with a primary endpoint representing the proportion of patients who develop skeletal metastases (International Standard Randomised Controlled Trial Number Register: 66626762).[69] Given the totality of this evidence, these agents should not be used outside of a clinical trial to delay bone metastases.

Radiopharmaceuticals

Targeting metastases with bone-seeking radiopharmaceuticals is a strategy that, until recently, has been reserved for the palliation of symptoms from osteoblastic and mixed osseous metastases, rather than for prolonging life. The beta-emitting agents strontium-89 and samarium-153 are both approved for pain palliation. These agents deliver ionized radiation to areas of increased osteoblastic activity by targeting the calcium hydroxyapatite in bone metastases. As a class of agents, the notable toxicity is myelosuppression as a result of damage to the surrounding bone marrow from radiation. This toxicity is typically transient in nature, but varies according to the characteristics of the radiopharmaceutical, such as half-life and scatter profile.

Strontium-89

Strontium-89 is a bone-seeking radiopharmaceutical that has well-established effects on pain palliation, with an overall response rate of 76%, according to a recent systematic review.[70] Although numerous trials have demonstrated improvement in pain both in prostate cancer and other solid tumors, only 1 study has demonstrated a survival benefit. Tu and colleagues randomized patients who responded to induction chemotherapy with ketoconazole, doxorubicin, estramustine, and vinblastine to receive consolidation therapy with doxorubicin every 6 weeks, with or without strontium-89.[71] The arm that received strontium-89 lived 10.9 months longer than the chemotherapy-only arm (16.8 months vs 27.7 months; *P*=.0014). This trial was small, however, and the chemotherapeutic regimen is not standard in prostate cancer.

Samarium-153

Another beta-emitter, samarium-153 conjugated to EDTMP, has several distinct properties in comparison to strontium-89 (as detailed in Table 3). The first randomized, double-blind, placebo-controlled study of samarium-153 was reported by Serafini and associates in 1998. It included various underlying malignancies involving bone, and demonstrated prompt pain relief at a dose of 1.0 mCi/kg that was durable at 16 weeks.[72] Sartor and colleagues later confirmed safety and pain efficacy in a purely metastatic prostate population.[73] The principal side effect observed in this study was a transient myelosuppression, with grade 3 or higher thrombocytopenia in 3% of patients and leukopenia in 5% of patients. Repeated dosing of samarium-153 1.0 mCi/kg every 8 weeks has also been shown to be safe and effective, although with increasing but reversible thrombocytopenia.[74]

Several more recent phase I/II trials pursued combination docetaxel, known to prolong survival, with samarium-153 in mCRPC.[75-77] The combination provides an appealing tumor and bone-directed strategy. Conceptually, the benefit and safety of combination therapy is indebted to these studies with beta-emitters; however, the use of a first-in-class alpha radiopharma-

Table 3. Comparison of Radiopharmaceutical Characteristics

	Strontium-89	Samarium-153-EDTMP	Radium-223
T 1/2 (days)	50.5	1.9	11.4
β energy	1.46	0.81	—
Gamma energy	—	0.103	—
Average range of tissue penetration (mm)	2.4	0.55	<0.1
Bone surface to red bone marrow dose ratio	1.6	4.4	10.3
MeV per decay	0.58	0.22	27.4

MeV=million electron volt; T 1/2=half life.

ceutical, radium-223, is leading contemporary studies of novel radiopharmaceuticals and multimodal therapy.

Radium-223

Radium-223, an alpha-emitting radiopharmaceutical, holds the greatest promise among bone-seeking radiopharmaceuticals for prolonged survival and a favorable toxicity profile. Alpha-emitters have a smaller depth of penetration in comparison to beta-emitters, with subsequently less marrow toxicity and count suppression. A phase I dose-escalation study using a single dose of radium-223 in 25 patients with breast or prostate cancer metastatic to bone identified only mild, reversible thrombocytopenia, with associated pain relief and declines in serum alkaline phosphatase, a measure of osteoblastic activity.[78] Pain improvement was seen in 60% of patients at week 4, while 20% of patients reported unchanged pain and 20% of patients reported worse pain. Although there were methodologic limitations to these pain assessments, such exploratory results are promising and compare favorably with other agents known to palliate pain in this disease. In a phase II trial, 64 patients with mCRPC received external beam radiation and were then randomized to receive placebo or 4 doses of radium-223 50 kBq/kg every 4 weeks. Changes in alkaline phosphatase differed significantly between the 2 groups (–65.6% for radium-223 vs 9.3% for placebo; $P<.0001$), and the toxicity profile was extremely favorable, with only mild thrombocytopenia.[79] A randomized, single-dose, dose-escalation, phase II trial of radium-223 in 100 patients with symptomatic mCRPC found in post hoc analyses that 71% of patients demonstrated a pain response at 8 weeks.[80] The favorable toxicity profile was confirmed. To date, radium-223 has been developed as an antitumor agent that can prolong survival, but the benefit of pain palliation has not been carefully studied.

In a combined analysis of 2 phase I trials and 3 phase II trials of radium-223 versus placebo, a 4.4-month overall survival advantage was seen in patients receiving radium-223,[81] leading to a randomized phase III trial in mCRPC. The international ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial, which had overall survival as the primary endpoint, randomized mCRPC patients to 6 doses of monthly intravenous radium-223 50 kBq/kg or placebo. The trial was stopped at a planned interim analysis because of evidence of a significant treatment benefit—a survival advantage of 2.8 months.[82] The ALSYMPCA trial did not assess for pain in a manner that could support an FDA regulatory label for pain palliation. This agent will be fast-tracked by the FDA and will seek a label on the basis of a survival advantage. As with other trials utilizing radiopharmaceuticals, there are ongoing studies assessing the safety and preliminary efficacy of combination radium-223 with other systemic therapy, such as docetaxel (NCT01106352).[83] This alpha-emitting radiopharmaceutical represents a breakthrough in the treatment paradigm for mCRPC, as this is the first large study to document improved survival by specifically targeting bone metastases.

New Therapeutics for Bone Metastases in Phase III Trials

Cabozantinib (XL-184)

Cabozantinib (Cometriq, Exelixis) is a tyrosine kinase inhibitor with particular inhibition of c-MET and vascular endothelial growth factor receptor 2 (VEGFR2). c-MET, a receptor for hepatocyte growth factor (HGF), is implicated in metastatic invasion to the bone and oncogenic processes in castration-resistant disease.[84-86] MET is highly expressed in bone metastases, and differentially so in comparison to primary localized prostate cancer and lymph node metastases.[87,88] In one pathology series, MET expression was detected in 40% of primary tumors, 54% of dissected lymph nodes, and 83% of metastases.[88] HGF is produced by bone marrow stromal cells and leads to c-MET activation and its downstream consequences.

Phase II studies of cabozantinib in mCRPC demonstrated remarkable effects on pain palliation and resolu-

tion of lesions on bone scintigraphy in an unprecedented manner.[89] Nearly half of patients were able to decrease or discontinue narcotics, and 86% had either partial or complete responses in bone lesions seen on bone scintigraphy at week 6. Over half of patients had more than a 50% decline in serum bone-specific alkaline phosphatase and plasma C-telopeptide, suggesting impact in bone turnover. The triad of improved symptoms, improved bone scan response, and improved markers of bone metabolism corroborate the hypothesis that cabozantinib is truly targeting the interaction between bone and tumor, and changing the microenvironment in ways that are reflected on bone scintigraphy. This has led to 2 phase III trials that are recruiting with separate primary endpoints; one will determine if cabozantinib has a survival advantage compared to placebo (COMET-1) and the other will measure amelioration of pain using patient-reported outcomes when compared to mitoxantrone (COMET-2). Aside from mitoxantrone and older beta-emitting radiopharmaceuticals, which arguably would not be FDA-approved by current standards, there are no contemporary agents approved on the basis of palliation of skeletal metastases, which makes this trial design and endpoint unique.

Conclusions

Prostate cancer's tropism for bone speaks to the complex bone-tumor interactions that allow for metastatic spread, as well as the often devastating clinical sequelae. For such reasons, studying the role of the supporting bone microenvironment is of continued scientific and therapeutic merit. Currently approved bone-directed therapies reduce SREs by inhibiting osteoclasts and palliate pain by targeting tumors in bone. As our understanding of the bone microenvironment evolves, the goals of novel bone and bone-tumor–directed therapies also seek to prolong survival for patients, as has been demonstrated with radium-223. Ongoing phase III clinical trials of cabozantinib will determine if a similar life-prolonging effect is demonstrable with this agent. Rational drug development can exploit the underlying pathophysiology of bone and its impact on tumor growth. Indeed, cross-talk between prostate cancer tumor cells and the bone milieu is integral to all stages of metastatic spread—from the initial homing of tumor cells to the bone through invasion and expansion of destructive metastases in the bone marrow. Disrupting these maladaptive signals with novel agents holds promise for their effects on skeletal metastases, and highlights the ongoing enthusiasm to target not only the seed, but also the soil.

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