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Review

Novel Approaches in the Pharmacotherapy of Skeletal-related Events in Metastatic Castrate-resistant Prostate Cancer

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Abstract. *Biphosphonates have long been the standard of care for antiresorptive treatment of bone metastases from castrate-resistant prostate cancer (mCRPC). Although the indication has historically been mostly palliative, response rates in skeletal-related events (SRE) remain low. Denosumab has been shown to be effective in prolonging time to first SRE in clinical settings, however, critical questions remain on its ability to affect bone metastases in mCRPC. The landscape for research progress in reducing SREs using novel pharmacotherapies is growing rapidly, with several agents in clinical trials. This focused review outlines the most promising investigational drugs for treating bone metastases in mCRPC.*

Prostate cancer is the most common malignancy among men and is associated with substantial morbidity and mortality (1). Although localized prostate cancer (PCa) is largely curable, a significant proportion of patients will go on to develop advanced, castrate-resistant disease. The skeleton is a preferred site for metastasis of PCa cells and is the primary cause of morbidity and mortality in metastatic castrate-resistant PCa (mCRPC). Current data suggests that approximately 33-46% of men with progressive castration-resistant nonmetastatic PCa will develop bone metastases at 2 years (2-3), whereas 90% of PCa-specific deaths occur with bone metastases (4). Outcomes in PCa with metastatic bone disease (MBD) is poor, with an approximate 1-year survival rate of only 40-47% (5) and a median survival of approximately 12-24 months (6).

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Our current understanding of the mechanisms of PCa cells metastasizing to bone has led to bone-targeted therapies for patients with PCa. The bone microenvironment represents a highly favorable site for tumor growth and invasion, involving a complex cellular interaction of osteoclasts, osteoblasts, endothelial cells, immunological cells and tumor cells. The steps leading to PCa metastasis are decreased local cell adhesion and detachment of cells from the primary tumor, invasion of the stroma, angiogenesis and intravasation into the vasculature, homing of cells to the vascular endothelium, and extravasation to bone marrow endothelial cells. Tumor growth in the bone microenvironment is fueled by growth factors released during osteoclastic bone resorption, such as insulin-like growth factor (IGF) and transforming growth factor beta (TGFβ). This supports proliferation of tumor cells and their release of growth factors that stimulate osteoblast growth and differentiation, including endothelin-1 (ET-1), bone morphogenetic proteins (BMPs), fibroblast growth factors, platelet-derived growth factor (PDGF) and interleukin-6 (IL-6). Additionally, both osteoblasts and PCa cells secrete factors that stimulate osteoclast activity, including receptor activator of nuclear factor-kappa B ligand (RANK-L), parathyroid hormone-related protein (PTHrP), and TGFβ (7-12). This multifaceted cross-talk between PCa cells, osteoblasts, and osteoclasts is considered a vicious cycle of bone metastasis in PCa (see Figure 1) (10).

Bone metastases reduce health-related quality of life in patients with PCa leading to skeletal-related events (SRE), such as pathological bone fractures, hypercalcemia of malignancy and spinal cord compression (13). (NCCN) clinical practice guidelines recommend either zoledronic acid or denosumab for prevention of SRE in mCRPC, but the preferred agent is unclear (14-15). Furthermore, the rate of SRE remains unacceptably high with the use of these agents, creating a need for continued development of novel therapies. A considerable amount of research is ongoing regarding *bis*phosphonates and

novel targeted therapies for prevention of SRE. This focused review will provide the clinician with an update on the pharmacotherapy of bone metastases in mCRPC.

Current Use and Development of FDA and EU-Approved Agents

Bisphosphonates: Teaching an old dog new tricks. The affinity and selectivity of *bis*phosphonates towards hydroxyapatite in the mineralized bone matrix makes them particularly attractive agents for managing skeletal metastases. Second-generation, nitrogen-containing *bis*phosphonates (*e.g.* pamidronate and zoledronate) are internalized by osteoclasts, whereupon they inhibit the key enzyme farnesyl pyrophosphatase, up-regulate pro-apoptotic molecules, and ultimately arrest osteoclastic bone resorption (16). Additionally, it has been suggested that *bis*phosphonates may have direct antitumor properties through a variety of mechanisms, including inhibition of angiogenesis, immunomodulation, and induction of apoptosis (17-21). Zoledronate, the most potent *bis*phosphonate currently available, has demonstrated the greatest efficacy in reducing the incidence of SRE in mCRPC. In a pivotal randomized controlled trial, zoledronate was associated with a significant reduction in SRE compared to placebo (44.2 *vs.* 33.2%, $p=0.021$) (22). However, a modest absolute decrease of 11% in the frequency of SRE has led researchers to explore new ways of utilizing these agents.

Recently, several novel *bis*phosphonate conjugates have been synthesized in order to couple the bone selectivity of *bis*phosphonates with the antitumor properties of more traditional chemotherapy. Many of these agents have shown potential in several pre-clinical models of bone metastasis. A gemcitabine/*bis*phosphonate conjugate was utilized in a murine model of human breast cancer bone metastasis and demonstrated a reduction in the number and size of bone metastases compared to a gemcitabine alone and an untreated control group (23). Several other *bis*phosphonate/chemotherapy conjugates have been synthesized that successfully inhibit a wide variety of human tumor cell lines, as well as osteoclasts, *in vitro* (24-25). Bisphosphonates have also been successfully incorporated into nanoparticles to facilitate cytotoxic drug delivery to bone metastases. In a murine breast cancer bone metastasis model, a nanoparticle consisting of a polymer and the *bis*phosphonate alendronate loaded with doxorubicin significantly reduced the incidence and size of skeletal metastases (26). Theoretically, this use of bone-targeted drug delivery of doxorubicin with *bis*phosphonates may also circumvent the considerable cardiotoxicity of this agent, although this has yet to be demonstrated in clinical trials.

Denosumab: Where does the RANK-L inhibitor rank? RANK expressed on the surface of pre-osteoclasts is activated by its ligand (RANK-L) which is expressed by osteoblasts and released by activated T-cells. The binding of RANK-L to RANK triggers osteoclast formation, activation, adherence, survival, and ultimately, bone resorption. Osteoprotegerin (OPG), a decoy receptor produced by numerous cell types (including osteoblasts), binds to RANK-L and prevents the RANK:RANK-L interaction, leading to a reduction in bone resorption. In PCa, metastatic tumor cells in the bone express RANK-L and also up-regulate its expression in osteoblasts (27). Thus, the critical interplay between RANK, RANK-L, and OPG in bone metabolism has become a desirable target for preventing SRE in mCRPC.

Denosumab is a fully human monoclonal antibody directed against RANK-L. A multicenter, international phase III trial conducted from 2006 to 2009 compared denosumab and zoledronic acid in the prevention of SRE in men with bone metastases in mCRPC. Results of the study, published in 2011, showed that denosumab was superior to zoledronate in delaying the time to first SRE (20.7 months *vs.* 17.1 months, $p=0.008$) and in the secondary endpoint of the cumulative mean number of SRE per patient (494 *vs.* 584 events; rate ratio =0.82, 95% CI 0.71-0.94, $p=0.008$). Adverse effects were similar between the two groups, although hypocalcemia was more common in patients receiving denosumab (13% *vs.* 6%, $p<0.0001$). The total number of patients who had a first on-study SRE, overall survival and disease progression were not statistically different between the two treatment arms (28).

Denosumab was approved by the FDA in 2010, and received approval in the EU in 2011 for the prevention of SRE in mCRPC. The cost-effectiveness of denosumab in the prevention of SRE been questioned considering the relatively modest absolute delay in the time to first SRE of only 3.6 months compared to the less-expensive zoledronate. A recent pharmacoeconomic analysis estimated that the 1-year and 3-year incremental total direct costs per SRE avoided with denosumab compared to zoledronic acid were $71,027 and $51,319, respectively. Because there is no commonly accepted willingness-to-pay threshold for cost per SRE avoided, the authors also conducted a cost-utility analysis using quality-adjusted life year (QALY) as the effectiveness outcome. Denosumab, when compared with zoledronic acid, was associated with a total incremental cost of $3.91 million per QALY gained at 1 year and $2.77 million per QALY gained at 3 years, indicating that the use of denosumab may not be cost-effective in the setting of mCRPC (29). The improvement in quality of life has also been questioned (30).

Denosumab is the first agent to show a significant benefit in delaying SRE compared to zoledronate. However, the modest efficacy and great expense of this agent may limit its clinical utilization. Moreover, *in vitro* data indicate that osteoclastogenesis can occur through pathways independent of RANK-L, which may explain the incomplete effect of denosumab in the prevention SRE (31). As such, the FDA Oncologic Drugs Advisory Committee voted to reject expanding the indication for

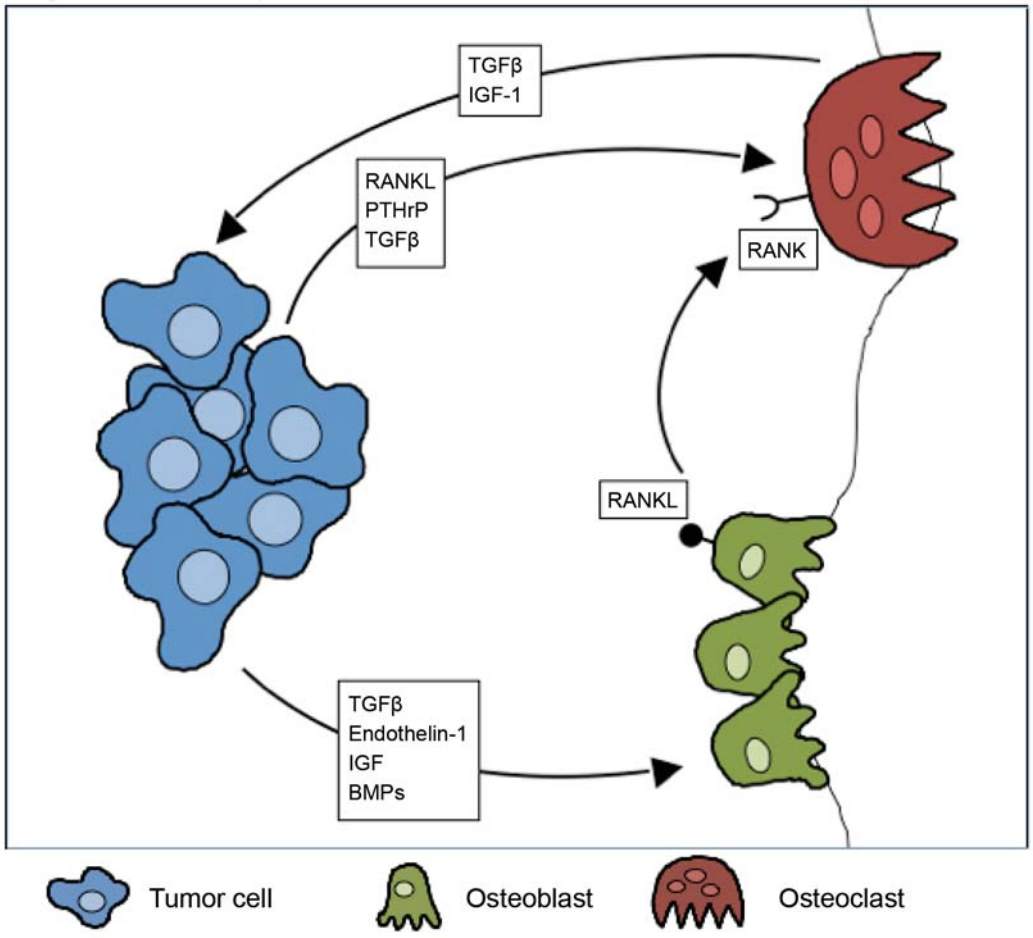

Figure 1. *Tumor cells secrete factors which contribute both to osteoblastic bone formation and osteoclastic bone resorption, which releases factors stimulating tumor growth causing a vicious cycle of osteolytic metastases. TGFβ: transforming growth factor beta, IGF-1: insulin-like growth factor 1, RANKL: receptor activator of nuclear factor-kappa B ligand, PTHrP: parathyroid hormone-related protein, RANK: receptor activator of nuclear factor-kappa B, IGF: insulin-like growth factor, BMPs: bone morphogenetic proteins.*

prophylaxis against bone metastasis in high-risk CRPC (32). Further research is necessary to characterize and target the alternative pathways of osteoclastogenesis, as well as to elucidate the effectiveness of combinations of denosumab and other antiresorptive agents in the prevention of SRE in mCRPC.

Radiopharmaceuticals: Bone-seeking targeted therapy. The clinical efficacy of bone-targeted radiopharmaceuticals has proven beneficial in palliative relief of bone pain. A recent Cochrane systematic review revealed that radiopharmaceuticals significantly increased the frequency of complete pain relief of skeletal metastases relative to placebo (risk ratio, RR=2.1) (33). The beta-emitting samarium-153 (sm153) and strontium-89 (sr89), the most commonly used agents, may also provide a survival advantage in mCRPC (34-35). A recent study evaluating the effect of sr89 plus docetaxel compared to zolendronate revealed that 73/101 mCRPC patients receiving docetaxel and sr89 successfully reached 6 months of chemotherapy (36), however, the trial is ongoing. A phase II trial combining docetaxel with sm153 has shown a median progression-free survival (PFS) of 6.4 months, with patients reporting long-term pain relief (37), whereas another trial reported a mean PFS of 7.5 months in taxane-naïve patients (38). Similar combination studies are also ongoing (39-40).

*Bis*phosphonates have been successfully utilized to enhance targeted radiotherapy of bone metastases. In an effort to improve the distribution and specificity of these agents to metastatic bone lesions, several radiopharmaceutical/*bis*phosphonate conjugates have been synthesized and have demonstrated superior biodistribution to bone compared to non-*bis*phosphonate-conjugated radioisotopes (41-43). Utilizing *bis*phosphonates as an innovative drug-delivery

mechanism for radiopharmaceuticals shows promise in the prevention of SRE in mCRPC, although studies in humans are needed to assess the true clinical efficacy and safety of these complexes.

Investigational Agents in Clinical Trials

Cathepsin K inhibitors. Cathepsin K is a cysteine protease expressed by osteoclasts that cleaves collagen I, the most abundant collagen in bone, and osteoclast adherence to the bone extracellular matrix is dependent on cathepsin K activity (44). Cathepsin K has also been shown to cleave the glycoprotein osteonectin, resulting in high-affinity peptides that stimulate tumor angiogenesis and invasion by cancer cells. Furthermore, bone tumors from PCa have been shown to up-regulate both osteonectin and cathepsin K (45). Thus, inhibition of cathepsin K represents a logical treatment modality for the prevention of SRE in mCRPC.

Odanacatib, an orally bioavailable selective cathepsin K inhibitor, has shown the most promise in clinical trials to date. Compared to other cathepsin K inhibitors (*e.g.* relacatib and balicatib), odanacatib is characterized by greater selectivity for cathepsin K and more potent inhibition, and by the absence of the morphea-like skin rash that has been reported in clinical trials with balicatib (44, 46). In a double-blind, randomized controlled trial in women with breast cancer and bone metastases, odanacatib was non-inferior to zoledronic acid in the suppression of urinary N-telopeptide of type I collagen (uNTx; a marker of bone resorption) over a four-week period (–77% *vs*. –73%) and was well tolerated (47). Further studies are required to determine if this biomarker reduction corresponds to a reduction in SRE, and unfortunately, clinical trials of odanacatib in the setting of mCRPC are currently lacking. Thus, although odanacatib remains a promising agent based on its efficacy in reducing biomarkers of bone resorption, the effectiveness of this agent for reducing SRE in mCRPC is unknown.

Inhibitors of the endothelin pathway. The endothelin pathway has emerged as a promising target for preventing SRE in mCRPC. The endothelins are a family of vasoactive peptides with varying patterns of distribution throughout the body. Endothelin-1, the most abundant endothelin, is expressed primarily by endothelial cells and exerts its effect by binding to one of two target receptors, ET_A or ET_B. Binding of endothelin-1 to ET_A triggers several signal transduction pathways, resulting in a broad range of physiological effects, while ET_B acts as a decoy receptor. In the setting of mCRPC, activation of ET_A contributes to angiogenesis, PCa proliferation and escape from apoptosis, and facilitation of the favorable skeletal microenvironment for tumor metastases (48). Additionally, endothelin-1 concentrations are significantly elevated in men with mCRPC, and the endothelin pathway has been shown to enhance the pain response in models of PCa-related pain (49). Atrasentan, an endothelin receptor inhibitor with preferential affinity for ET_A, has shown promising activity in phase I and II trials in mCRPC, demonstrating decreases in cancer-related pain, a reduction in prostate-specific antigen (PSA) levels, and decreased time to disease progression compared to placebo (50-51). However, a multinational phase III trial of 809 men with mCRPC found that although atrasentan resulted in a significant decrease in bone alkaline phosphatase (BAP) and PSA, it did not delay time to disease progression compared to placebo. Disease progression in this study was defined as any evidence of radiographic or clinical progression, and SRE were one component of the definition of clinical progression in this study. Interestingly, researchers reported that the majority of disease progression events resulted from radiographic progression, and 87% of radiographic progression events occurred in the absence of any study-defined clinical progression (52). Thus, although atrasentan did not meet the primary outcome of time to any disease progression, this study does not rule out the potential efficacy of this agent in the prevention of SRE.

In contrast to atrasentan, zibotentan, another ETA inhibitor in clinical development, does not bind to the ET_B decoy receptor (53). Phase I studies of this agent alone and in combination with docetaxel for mCRPC have revealed that the agent is well-tolerated, with headache, peripheral edema, fatigue, nasal congestion and nausea as the most frequent adverse effects (53-54). A phase II trial of 312 patients with mCRPC and bone metastases who were pain-free, or mildly symptomatic for pain, failed to demonstrate an advantage of zibotentan in the primary outcome of time to progression. However, patients treated with either dose of zibotentan experienced a significant improvement in median overall survival compared to placebo [24.5 months (10 mg) and 23.5 months (15 mg) *vs*. 17.3 months] (55). An extended follow-up of patients enrolled in the phase II trial confirmed the benefit of zibotentan on median overall survival. Zibotentan at 15 mg and 10 mg were associated with non-significant reductions of 24% (HR, 0.76; 80% CI, 0.61–0.94; p=0.103) and 17% (HR, 0.83; 80% CI, 0.67-1.02; p=0.254), respectively, in the risk of death compared to placebo (56). Loss of significance in the follow-up analysis could be due to the early time-to-progression observed in the study, causing patients to stop treatment. Kaplan–Meier curves support this hypothesis, as the curves for placebo and zibotentan become parallel at cessation of treatment for most patients (56). Of particular interest in the prevention of SRE, treatment with zibotentan at 10 mg resulted in a significant reduction in bone metastases at study discontinuation compared to placebo. The 15 mg dose was no different from placebo in this regard, although the number of bone metastases at baseline was higher at 15 mg dose, compared to 10 mg and placebo (56). Phase III trials of zibotentan in mCRPC, both alone (ENTHUSE M1, NCT00554229) and in combination with

docetaxel (ENTHUSE M1C, NCT00617669) have been completed, which will likely shed further light into the clinical utility of this agent in preventing SRE.

Matrix metalloproteinase (MMP) inhibitors. MMPs are proteases that degrade the extracellular matrix, facilitating tumor metastasis and angiogenesis. MMPs are overexpressed in the setting of mCRPC, and there is evidence that PCa cells themselves secrete MMPs which aid in the degradation of the mineralized bone matrix (57). Early-generation MMPs were associated with significant musculoskeletal toxicity, limiting their clinical usefulness. This toxicity has been attributed to inhibition of non-MMP proteases [including those of the (ADAM) and (ADAMTS) families] and their associated sheddase activity (58).

Rebimastat (BMS-275291) is a broad-spectrum MMP inhibitor devoid of toxicity-related inhibition of sheddases. A phase I trial of rebimastat in patients with advanced or metastatic cancer found the drug to be well-tolerated; arthralgia, myalgia, rash, fatigue, headache, nausea, and dysgeusia were the most common adverse reactions, all of which were grade 1 or 2 (58). Unfortunately, a phase II trial comparing two different doses of rebimastat in 80 patients with mCRPC demonstrated a disappointing lack of efficacy, with a median PFS of only 1.8 months (59). Investigators were unable to obtain serial measurements of bone resorption markers, and it remains to be seen whether rebimastat can prevent SRE in mCRPC.

Tyrosine kinase inhibitors. Although metastatic tumor growth is supported through induction of angiogenesis, inhibition of receptor tyrosine kinase pathways have not been extensively evaluated in clinical trials of mCRPC. This is likely due to only moderate responses (60-63) or negative effects in the mCRPC setting (64). Inhibition of the nonreceptor tyrosine kinase SRC with dasatinib, however, has proven to be an effective approach for inhibiting bone osteolysis due to PCa metastases (65). In a phase II study of dasatinib monotherapy in mCRPC, responses were encouraging, with significant reductions in the bone resorption markers uNTx and serum BAP in the majority of patients (66). Combination studies of dasatinib with docetaxel have also shown promise in mCRPC, with 14 out of 46 patients experiencing a disappearance of a lesion on bone scan, and 87% of patients with decreases in uNTx (67). In a phase I study of the SRC inhibitor saracatinib in healthy men, markers of bone resorption decreased significantly in a dose-dependent manner (68). Another SRC inhibitor, bosutinib, causes dramatic reductions in bone lesions in preclinical models (69), but saracatinib and bosutinib have yet to be evaluated in human clinical trials of mCRPC (70-71).

Bone metastases are also associated with increased expression of tyrosine kinase (MET), and cabozantinib (XL184) is a dual-targeted agent that blocks both MET kinase and vascular endothelial growth factor receptor-2. In preliminary data from phase II studies, high rates of objective response with complete or partial regression of bone metastases in 75- 85% of patients have been reported (72-73). Moreover, median PFS in docetaxel-prereated and docetaxel-naive patients was 24 and 29 weeks, respectively, with improved pain in 67% patients with painful bone metastases. The majority of patients had reductions in bone turnover markers; however, this was not consistent with objective responses (74). Overall, cabozantinib appears to be clinically active in mCRPC.

Alpha-emitting radiopharmaceuticals. Changing the landscape of radionuclide therapy are ongoing investigations with the alpha-emitter, radium-223 (^{223}Ra), which irradiates tumors over a more limited range compared to beta-particle emitters. ^{223}Ra has a tumor to bone marrow absorbed dose ratio of 30:1, which is expected to result in reduced myelosuppression (75). In a phase II trial of ^{223}Ra in symptomatic patients with mCRPC, ^{223}Ra was effective and exceptionally well tolerated, with a median time-to-progression of 26 weeks, accompanied by significant reductions in BAP (76). The phase III placebo-controlled ALSYMPCA trial was discontinued early due to clear evidence of a significant treatment benefit with ^{223}Ra. ^{223}Ra delayed the time to SRE from 8.4 to 13.6 months and also significantly prolonged overall survival in symptomatic patients with mCRPC (14 months *vs*. 11.2 months; p=0.000185) (77). It was also reported that dose-dependent normalization of BAP is associated with the survival benefit (78).

Conclusion

SRE in mCRPC are a significant clinical problem, resulting in considerable patient morbidity and mortality. FDA-approved agents for the prevention of SRE, namely the *bis*phosphonate zoledronate and the RANK-L inhibitor denosumab, have only resulted in modest reductions in the incidence of SRE. The relative efficacy and safety of the cathepsin K inhibitor odanacatib and the ET_A inhibitor zibotentan in phase I and II trials has underscored the need for further investigation of these agents, either alone or in combination with other proven therapies for mCRPC. Despite the paucity of robust, phase III clinical trial data with these investigational agents, much progress has been made towards developing novel therapeutic strategies aimed at reducing SRE in mCRPC.

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