Evolution of Treatment Options for Patients With CRPC and Bone Metastases: Bone-Targeted Agents That Go Beyond Palliation of Symptoms to Improve Overall Survival

This review will examine agents with potential activity in the palliation and treatment of skeletal metastases of prostate cancer, and will weigh the clinical-outcomes evidence for and against their broad use.

Introduction

Metastasis to bone represents a frequent complication of advanced-stage prostate cancer (PCa). The exact prevalence of bony metastasis is generally unknown, but some estimate that 50% to 70% of patients with advanced-stage PCa will ultimately develop this devastating complication.[1,2] PCa preferentially metastasizes to the axial skeleton, including the vertebrae, pelvis, proximal ends of long bones, and skull.[3] The resulting skeletal complications are widely recognized to increase mortality and decrease quality of life, since affected patients suffer loss of independence, mobility, and social functioning (Figure 1). The clinical consequences of skeletal metastasis also include pain, skeletal-related events (SREs), and increased costs of therapy. Recent advances in our understanding of the mechanisms of metastasis and of the physiologic changes that occur along with it, along with the introduction of new treatments, are improving our ability to combat this problem.

FIGURE 1

The Negative Impact of Bone Complications

There are several important characteristics of bone that implicate it as the preferential site for metastasis of visceral cancers. In 1889, Stephen Paget first noted in his “seed and soil” hypothesis that the complementary characteristics of target organs and circulating tumor cells would determine where tumors metastasize.[4] Bone has high blood flow to marrow, where many important growth factors and cytokines reside and are involved in the constant remodeling of bone; these factors include transforming growth factor β, endothelin-1, interleukin (IL)-1 and IL-6, prostaglandins, insulin-like growth factors, fibroblast growth factors, and platelet-derived growth factors.[5] The final necessary step in metastasis involves tumor cell expression of adhesive molecules. The bone microenvironment milieu provides the perfect environment for tumor cell deposition and clonal expansion.

Skeletal pain from metastasis manifests as a deep nonspecific ache that worsens with movement and that can be quite severe; it progresses as metastatic disease progresses. Patients usually start on nonsteroidal anti-inflammatory drugs (NSAIDs), move to opioids, and then require more advanced, systemic palliation therapies, which will be reviewed here. Some early studies mentioned in the sections below measured the palliative effects of an intervention using pain scale...
questionnaires or diaries, opioid usage (either prescribed or patient-reported usage), patient-reported sleep patterns, or even doctor-reported pain scores. As the reader may realize, some of these measures are highly subjective and vary from patient to patient, making the comparison of different studies more difficult.

TABLE

Trials of Treatments for Castration-Resistant Prostate Cancer

Unfortunately, few treatments specifically target tumor cells that reside in bone, and those that are available have drawbacks related to dose-limiting toxicities and may have only small therapeutic benefit. Further, patients who have exhausted chemotherapeutic options or who do not tolerate their side effects find themselves with a limited number of treatment options after the diagnosis of skeletal metastasis. This review will examine agents with potential activity in the palliation and treatment of skeletal metastases of PCa, and will weigh the clinical-outcomes evidence for and against their broad use (Table).

Targeted Treatments for Symptom Palliation

Bisphosphonates

Bisphosphonates target the osteoclastic feedback loop that develops between a metastatic lesion and bone, thereby preventing or delaying the onset of SREs.[6,7] These drugs bind to the active site of bone resorption and turnover, enter osteoclasts, disrupt cellular signaling pathways, induce apoptosis, and prevent further resorption.[8] The goals of bisphosphonate therapy include increasing bone mineral density (BMD), preventing new and recurrent SREs, palliating bone pain, reducing the need for other therapies, and mitigating further morbidity. The efficacy of this class of drug in attaining these clinical goals has been investigated in multiple placebo-controlled randomized trials, which have shown significant improvements in clinical outcomes with these agents.[9-11] Zoledronic acid (Zometa) is a bisphosphonate approved for the prevention of SREs in men with metastatic castration-resistant prostate cancer (CRPC). Its role was established by a study of men with metastatic CRPC by Saad et al, in which 4 mg of zoledronic acid was given every 3 weeks; the incidence of SREs was reduced from 44% in the placebo arm to 33% in the zoledronic acid arm.[12] Follow-up phase II trials have examined other dosing regimens, such as 4 mg every 3 months—or even yearly—and have demonstrated preservation of BMD in men receiving androgen-deprivation therapy (ADT), but these studies did not specifically examine outcomes involving SREs.[13,14] Bisphosphonates, when used for the treatment of debilitating bone pain, reduce the need for NSAIDs and opioid analgesics, which can have unintended consequences for patients with advanced cancer. Zoledronic acid is administered intravenously. Despite its systemic activity, it lacks the myelosuppressive side effects of chemotherapy or radiation, and it can be used as an adjunct to such therapies. Bisphosphonates have never been shown to prevent metastasis, but they do offer prevention of their deleterious effects and mitigation of SREs and bone pain. Some studies have demonstrated in vitro synergistic cytotoxic effects between bisphosphonates and chemotherapies, but these have never been borne out in clinical studies.[15,16]
The Vicious Cycle of Bone Destruction From Metastases: the Role of RANK Ligand—

**Human monoclonal antibodies**

Denosumab (Xgeva) is a fully human monoclonal antibody against receptor activator of nuclear factor-κB ligand (RANKL); it disrupts the normal homeostatic messaging that occurs between osteoblasts and osteoclasts in bone, and its administration causes a decrease in bone turnover and resorption (Figure 2). Denosumab has been well studied in several clinical areas that involve bone loss, including in postmenopausal women and in men with CRPC. It is currently FDA-approved for use in both postmenopausal women and men with advanced prostate cancer and bone metastasis, to prevent bone loss and subsequent fracture.[17,18] The latter group presents a particular challenge with respect to potential loss in BMD and subsequent SREs for several reasons, including prolonged use of ADT and/or development of skeletal metastasis. Below we highlight several of the key studies of denosumab that have been published to date.

In a phase II trial of denosumab in patients with bone metastases from prostate, breast, and other cancers who were noted to have persistently elevated bone turnover markers (urinary N-telopeptide [uNTx]) while receiving intravenous (IV) bisphosphonate treatment, patients were randomly assigned to receive subcutaneous denosumab or continuation of the IV bisphosphonate. This study noted that more patients achieved normal levels of urinary bone turnover markers (about 64% vs 37%; \( P = .01 \)) and that patients experienced fewer SREs (8% vs 17%; odds ratio [OR], 0.31; 95% confidence interval [CI], 0.08-1.18) with denosumab than with bisphosphonate treatment. Similar numbers of patients suffered adverse events in the two arms.[19]

In 2009, Smith et al published the results of a phase III randomized controlled trial comparing denosumab to placebo in patients with nonmetastatic PCa who were receiving ADT. The key endpoints were percent change in BMD in the lumbar spine, total hip, and femoral neck at 24 and 36 months, and incidence of new vertebral fractures.[20] Lumbar spine BMD increased by 5.6% in the treatment group as opposed to a BMD decrease of 1.0% in the placebo arm (\( P < .001 \)). Patients who received denosumab also experienced a decreased incidence of new vertebral fractures at 36 months (1.5% vs 3.9% with placebo) (relative risk, 0.38; 95% CI, 0.19 to 0.78; \( P = .006 \)). Subsequent analyses noted that patients with high baseline levels of turnover markers (serum C-telopeptide and tartrate-resistant alkaline phosphatase 5b) had the greatest increases in BMD.[21]

Phase III studies comparing denosumab to the bisphosphonate zoledronic acid with respect to time to development of a first SRE in patients with CRPC and at least one bone metastasis were published in 2010.[22,23] Denosumab improved the median time to development of a first SRE (20.7 months vs 17.1 months for zoledronic acid, a difference of 3.6 months). Rates of osteonecrosis of the jaw were not significantly different between the two study arms, at 2.3% and 1.3%, respectively (\( P = .09 \)), but hypocalcemia was observed more frequently with denosumab than with zoledronic acid (13% vs 6%). This report showed no difference in overall survival between the two groups. Recently, results were presented regarding the ability of denosumab to prevent the development of bone metastasis.[24] Some have hypothesized that, by limiting bone turnover and resorption, denosumab may make bone an environment that is less amenable to circulating tumor cells remaining and clonally expanding. In this report by Saad et al, denosumab increased the time to development of first bone metastasis by a median of 4.2 months compared with placebo, in a population of men deemed to be at high risk for development of metastatic disease. No difference in overall survival was noted, however.

In summary, denosumab is a fully human monoclonal antibody against RANKL; it inhibits osteoclast activity, limiting bone turnover and resorption. It is approved for the prevention of SREs in high-risk postmenopausal women and men with advanced prostate cancer and bone metastasis. Denosumab does not have any direct antitumor activity, and while there is some recent evidence that denosumab prevents development of bone metastasis, it has not yet been approved for this use. Studies published to date have demonstrated its ability to help prevent and reduce SREs in men with
and without bone metastasis, compared with bisphosphonates and placebo, to increase BMD over placebo, and to improve the time to development of a first SRE compared with zoledronic acid. Clinicians will ultimately have to grapple with cost-benefit issues, since denosumab is more expensive than zoledronic acid. Clinicians will also have to weigh the convenience of a subcutaneous injection of denosumab against the intravenous administration of zoledronic acid and fewer cases of renal toxicity with denosumab. As mentioned, in a head-to-head study, denosumab delayed SREs by 3.6 months compared with zoledronic acid.

**Beta-emitting radionuclides**

Patients with multifocal metastases from visceral cancers, primarily breast and prostate, have long had their symptoms palliated with radiopharmaceuticals. These patients typically suffer marked decreases in quality of life as a result of pain, which has been described as "deep nonspecific ache rising in intensity as the disease progresses, incident pain on movement (alldynia), which renders patients virtually immobile, and spontaneous pain that can be severe."[25] Patients generally progress from NSAIDs to opioids, and then to more advanced, systemic palliation therapies.

**Mechanism of action, side effects, range, and safety considerations.** While discrete sites of metastasis can be amenable to external beam radiotherapy for the palliation of pain, diffuse bony metastatic disease requires agents that preferably localize to bone, have limited toxicity but long enough half-lives to kill tumor cells, have favorable pharmacokinetic properties, and are safe to handle. To date, phosphorus-32, strontium-89 (Metastron), samarium-153 (Quadramet), rhenium-186, and rhenium-188 have all been used in this setting. [26]P was noted early on to cause marked bone marrow suppression and thus is not used or approved for clinical use.[26] The beta particles (which consist of electrons) emitted by these radioisotopes cause the destruction of malignant cells through DNA damage and the induction of apoptosis. They have a relatively low, linear energy transfer (LET) radiation that tracks 2.5 to 11 mm.[25] The limited range of these particles minimizes danger to healthcare personnel, but the deceleration of beta particles as they pass through shielding (eg, lead) can result in the formation of more dangerous, high-energy x-rays. In addition to emitting beta particles, $^{153}\text{Sm}$, $^{188}\text{Re}$, and $^{186}\text{Re}$ also decay to gamma photons, allowing for external monitoring of radionuclide biodistribution after administration. Bone marrow suppression, primarily in the form of thrombocytopenia and leukopenia, is the most common side effect seen with clinical use. $^{89}\text{Sr}$ and $^{153}\text{Sm}$ are FDA-approved for the palliation of bone pain associated with metastasis, while $^{186}\text{Re}$ and $^{188}\text{Re}$ are still considered experimental.

**Strontium-89.** The therapeutic benefit of $^{89}\text{Sr}$ was first established in 1942 by Pecher, who administered 3 doses over 5 months to a patient with advanced prostate cancer metastasized to bone.[27] The patient was noted to have an excellent clinical and radiographic response. Since that time, many observational and randomized controlled trials examining the use of $^{89}\text{Sr}$ have been published. Strontium sits below calcium in the periodic table, and it thus follows the path of calcium in the human body and localizes to areas of bone where calcium turnover is the greatest. In general, although subjective pain scales and definitions of responders differ between many of these studies, published reports have largely demonstrated that the palliative effect of $^{89}\text{Sr}$ is substantial (absolute risk reduction for achieving pain relief, 0.321; 95% CI, −0.035 to 0.678) and not secondary to a placebo effect.[28] Comparison of $^{89}\text{Sr}$ and local external beam radiation showed similar response rates but no difference in overall survival.[29]

**Samarium-153.** $^{153}\text{Sm}$ was approved by the FDA in 1997 for palliation of pain from cancer metastasized to bone. The radioactive element is chelated to ethylenediaminetetramethylenephosphonic acid to form $^{153}\text{Sm}$-EDTMP. This compound is cleared renally within 6 hours of intravenous administration. The element itself has a half-life of 1.9 days, but it is cleared from the blood with a t_{1/2} of 5.5 minutes. Although its mechanisms of targeting bone are not completely understood, $^{153}\text{Sm}$ preferentially accumulates and associates with hydroxyapatite crystals in areas of high bone turnover. Examinations of metastatic lesions have noted concentrations of $^{153}\text{Sm}$ that are five times those seen in normal tissue, thus exposing these tumors to greater amounts of radiation and protecting healthy tissues. The range of emitted beta particles from $^{153}\text{Sm}$ is only 0.5 to 3 mm, shorter than that for beta particles from $^{89}\text{Sr}$.

Multiple observational studies have reported improvements in pain scores for patients with bony metastases from CRPC. Phase II randomized controlled trials have demonstrated that higher doses of $^{153}\text{Sm}$-EDTMP (37 megabecquerel/kg) were more effective than lower doses (18.5 megabecquerel/kg) or placebo at lowering pain scores and reducing analgesic use.[30,31] A phase III randomized controlled trial randomly assigned patients to receive either radioactive $^{153}\text{Sm}$-EDTMP or nonradioactive 152
Sm-EDTMP. The investigators noted significant reductions in analgesic use in the active treatment group at 4 weeks, 9% of complete responders had a greater than 50% reduction in serum prostate-specific antigen (PSA), and myelosuppression accounted for the majority of side effects.[32] Sartor et al also demonstrated that $^{153}$Sm-EDTMP can be safely redosed in patients after loss of analgesic effect.[33]

Comparisons of various beta emitters. Multiple studies have performed head-to-head comparisons of different beta particle-emitting radionuclides reviewed here.[25] No clinically significant differences in pain, analgesic usage, or performance status have been noted. Recommendations to date have maintained that clinician or patient preference, ease and safety of handling, pharmacokinetics, and cost remain the primary determinants of which therapy should be used. There have been shortages in supplies of radionuclides in recent years, and this may pose some limitations on the choice of radiopharmaceutical.

Beta emitters in combination with chemotherapy and bisphosphonates. Although beta particle-emitting compounds have shown mixed data with regard to PSA response rates after therapy, researchers have investigated combinations of these radioactive, bone-targeted therapies with chemotherapeutic drugs and/or bisphosphonates to determine whether any synergistic effects might be seen. Several have hypothesized that the radiation might sensitize tumor cells to further damage by chemotherapeutic agents. A phase II trial randomly assigned patients to chemotherapy either with or without $^{89}$Sr. Overall survival improved considerably in the combination arm compared with chemotherapy alone (28 vs 17 months).[34] Another phase II trial examined the combination of docetaxel and $^{153}$Sm-EDTMP in men with bone metastases from CRPC: PSA response was seen in 77%, pain response was seen in 69%, and the combination was well tolerated.[35] The primary endpoint was PSA progression-free survival, which was 6.4 months, with all patients ultimately relapsing. Median survival was 29 months.

In summary, these agents offer palliation of pain and can reduce opioid use. While the radiation produced by these compounds is cytotoxic, PSA response is not the primary indicator of effect, and no study has shown these compounds by themselves to affect overall survival. They are relatively well tolerated, with the most common side effect being myelosuppression that is reversible. These drugs may be re-dosed for continued effect, and combinations with other accepted treatments for metastatic CRPC may provide synergistic effects. Given the concerns regarding radiation safety of clinical personnel and patients, they should always be administered in special facilities by qualified personnel.

External beam radiation therapy

Bony metastasis of primary cancers results in considerable morbidity for patients, primarily causing pain, neurologic and functional sequelae, and hypercalcemia.[36] External beam radiotherapy has been a mainstay of palliation and treatment for these lesions, but the exact mechanism of action is not well defined. The doses required to provide pain relief are far less than those required to destroy tumorous lesions, implying effects on bone homeostasis and alteration of signaling pathways involved in bone turnover. Palliative goals of external beam radiotherapy include improvement in quality of life through pain reduction, prevention of further bone destruction, maintenance of the functional capacity of the patient, and prevention of neurologic sequelae, particularly in metastases to the spinal column.

Most studies report complete or partial pain relief in 70%, with 40% to 60% of those reporting partial relief. Onset of relief is variable, ranging from as soon as 48 hours after therapy to 4 weeks. Focal therapy can treat single lesions confirmed by imaging and correlated with patient symptoms. Considerations of site, surrounding tissues, margin, performance status, and current hematologic parameters should be taken into account when making decisions regarding treatment volume and dosing. Hemibody radiation should be considered in patients with multiple metastases. One trial compared local radiation to local radiation plus hemibody radiation. Development of new, symptomatic lesions was similar between the two groups, but time to progression was significantly longer in the combination group (12.6 vs 6.3 months).[37]

The optimum dose and timing of delivery has been a hotly contested issue, but a meta-analysis showed no significant differences between the different schedules.[38] A review of 12 randomized trials on the duration of pain relief and median overall survival by Ratanatharathorn et al largely concluded that no patients had durable responses that lasted the remainder of the life of the patient and that higher doses trended to the greatest pain relief.[39] With respect to the cost-benefit ratio of a single-fraction dose (4 to 8 Gy) vs multifraction higher doses of radiotherapy (30 to 45 Gy total), this meta-analysis concluded that while the former does provide some relief in a large percentage of
patients, the higher-dose fractionated regimens were much better. In the United States, a survey of radiation oncologists showed that most employ 30 Gy in 10 fractions.[40]

**Nontargeting Treatments That Improve Survival and/or Palliate Symptoms**

**Systemic chemotherapy**

The development and use of cytotoxic chemotherapies for the treatment of advanced PCAs has lagged behind parallel advances in other common cancers. In the 1990s, mitoxantrone (Novantrone) in combination with prednisone was approved for the treatment of advanced prostate cancer, based on improvement in palliative and quality of life measures.[41] The paper by Tannock et al, on which the approval was based, noted that at the time, chemotherapy for these patients was controversial given the frequently seen unwanted secondary effects offsetting pain relief. Prior to this study, the coadministration of corticosteroids muddled cause and effect, since their use alone had also been shown to offer palliation of symptoms from metastatic disease. The Tannock study, however, proved that chemotherapy (mitoxantrone) plus prednisone provides better palliation than prednisone alone. Since that time, however, several cytotoxic agents have been or are being considered for approved use in patients with CRPC with and without metastasis. In general, this class of agents acts systemically, and their direct cytotoxic activity is not specific to metastatic sites and affects healthy tissues. Chemotherapeutic toxicities and natural and acquired drug resistance remain unresolved issues. Furthermore, objective measurement of response to therapy at metastatic sites remains difficult; although it can be performed radiologically, the classification of response requires radiologist knowledge of the criteria (eg, RECIST [Response Evaluation Criteria In Solid Tumors]).

Many of the studies simultaneously report on palliation, but as with the beta particle–emitting radionuclide class of compounds, measures of palliation are more subjective and highly variable between studies. Moreover, these symptomatic outcomes do not reliably indicate tumor regression or reduction in overall disease burden.

To date, most clinicians and study investigators have used serum PSA as a marker of outcome; however, there have been numerous reports of the deficiencies of this marker in the case of cancer immunotherapy.[42,43] Namely, although some prostate cancer immunotherapies have been shown to improve overall survival, they have had little or no impact on PSA kinetics, sometimes even increasing PSA levels despite positive therapeutic effect. Some groups have advocated the use of circulating tumor cells (CTCs) as a marker, where a count of ≥ 5 CTCs/7.5 mL of blood has been shown to correlate with worse outcome compared with < 5 CTCs/7.5 mL of blood.[44]

Despite these hurdles with respect to determining outcomes in patients with metastatic disease, the data clearly show that chemotherapies such as docetaxel and cabazitaxel (Jevtana), and immunotherapy with sipuleucel-T (Provenge), improve overall survival—largely the best measure of cytotoxic effect. To date, there has been relatively little focus on responses in patients with bone metastasis or on survival as a function of extent of bony disease. We are, however, beginning to understand which compounds work best as first-, second-, and third-line agents. After the approval of docetaxel, there had been no clear standard of care in the second-line chemotherapy setting. Mitoxantrone was used, but its activity after progression on docetaxel is modest.[45] The development of newer agents that are examined in different patient classes—such as those who are chemotherapy-naive or chemotherapy-resistant—promises to open up advanced PCAs to many new forms of treatment.[46]

**Docetaxel.** In 2004, docetaxel plus estramustine (Emcyt) was reported to yield an improvement in survival compared with mitoxantrone and prednisone, in men with metastatic, advanced CRPC.[47] Median time to progression, defined as two consecutive increases in PSA level over baseline or an interval increase in a bidimensionally-measured lesion, was 6.3 months in those receiving docetaxel and estramustine and 3.2 months in the group given mitoxantrone and prednisone (P < .001). Despite an improvement in overall survival (17.5 months vs 15.6 months, P = .02), no significant differences were noted in measurable disease or pain between the two groups.

Tannock et al compared docetaxel and prednisone, given every week or every 3 weeks, to mitoxantrone and prednisone administered every 3 weeks.[48] This study showed a statistically significant improvement in survival (of approximately 3 months), and it demonstrated improvements in reported pain levels. No efficacy with respect to disease progression was reported in this study. Mature follow-up data comparing mitoxantrone to docetaxel given every 3 weeks confirmed the 3-month survival advantage of the earlier study.[49] On the basis of these data, docetaxel chemotherapy has become the standard first-line chemotherapy treatment for advanced CRPC.

**Cabazitaxel.** This microtubule inhibitor with a mechanism of action similar to that of docetaxel was
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CRPC that is asymptomatic or minimally symptomatic. Because the focus of this review is palliative survival.[56,58] Sipuleucel-T was approved by the FDA in April 2010 for the treatment of metastatic CRPC. About 80% of patients had bony metastasis, 50% had measurable soft-tissue disease, and 25% had visceral lesions. The authors did not break out results with respect to palliation of bone pain or disease progression as a function of bone metastasis, which would likely have been difficult in this patient population with mixed bony, visceral, and soft-tissue disease; interpretation of the results with respect to specific treatment of bony disease is thus difficult.

Bone marrow suppression was observed in those treated with cabazitaxel, who experienced a 7.5% incidence of febrile neutropenia compared with 1.3% in those treated with mitoxantrone. There was an increased risk of death within 30 days of last dose in the cabazitaxel-treated patients (5%) compared with the risk in the mitoxantrone-treated patients (2%). Bone marrow suppression can be minimized by granulocyte colony-stimulating factor support. Study investigators recommend close monitoring of patients and future investigation into possible single-nucleotide polymorphisms in genes such as CYP3A4 and CYP3A5, which are responsible for the metabolism of cabazitaxel and which may contribute to such toxicities.

Immunotherapies

Sipuleucel-T. In the late 1990s, researchers began to investigate the concept of tumor-specific immunity, whereby an immune response is stimulated in order to target tumor cells for destruction.[53] This idea was central to the development of sipuleucel-T. In the course of treatment with sipuleucel-T, a patient’s antigen-presenting cells (APCs; specifically dendritic cells) are collected via leukapheresis and then loaded ex vivo with a fusion protein consisting of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF). After culturing this fusion protein with the dendritic cells, the product is then reinfused into the patient, activating T-cells via class I and class II HLA molecules and resulting in a beneficial immune response against PAP.

Initial studies found PSA level to be a poor marker of clinical response in the case of sipuleucel-T.[54] To address this potential inadequacy of PSA levels, investigators altered the definition of “progression” from a biochemical change (in PSA level), to objective enlargement of soft tissue disease or the appearance of two or more new lesions on radionuclide bone scan. Using this new definition, median time to progression in a phase II study was 118 days.[55] A phase III trial enrolled 127 asymptomatic men with metastatic CRPC randomized in a 2:1 ratio to receive either sipuleucel-T or placebo.[56] Interestingly, there was no significant difference in time to progression between the two treatment arms, but there was a 4.5-month improvement (P = .01) in overall survival in the sipuleucel-T arm. However, this study was not originally designed to detect an increase in overall survival.

To bolster proof of clinical efficacy, investigators proceeded with a second phase III, double-blind, placebo-controlled, multicenter trial of sipuleucel-T that was designed to measure its effect on overall survival.[57] In this trial, 512 patients were randomized in a 2:1 ratio to receive either sipuleucel-T or placebo. The study detected a 4.1-month improvement in overall survival compared with placebo, despite allowing 109 of 171 patients in the placebo group to cross over and receive salvage sipuleucel-T (prepared and cryopreserved at the time of placebo preparation). Adverse events in the treated group were primarily limited to fever, chills, and headache at or near the time of the infusion. Similar to previous studies, there were no differences in the time to disease progression (measured radiographically at 6, 14, 26, and 34 weeks, and every 12 weeks thereafter) between the two groups.

Investigators attributed the discordance between the observed survival benefit and the lack of effect on disease progression to a possible class effect, since a similar phenomenon has been reported in a study on poxviral-based PSA-targeted immunotherapy (PROSTVAC-VF).[43] Other studies of metastatic CRPC have also shown a lack of correlation between disease progression and overall survival.[56,58] Sipuleucel-T was approved by the FDA in April 2010 for the treatment of metastatic CRPC that is asymptomatic or minimally symptomatic. Because the focus of this review is palliative...
treatment of metastatic disease, we point out that there is currently no evidence to support the use of sipuleucel-T in symptomatic patients.

**Emerging Bone-Targeted Agents That Go Beyond Palliation and May Improve Survival**

**Src inhibitors**

Src is a member of the largest family of protein tyrosine kinases, the Src family kinases (SFKs). Src has been widely implicated through increased expression and/or activity in many visceral cancers, including prostate cancer. In addition, Src has been implicated in proliferation, invasion, and migration of prostate cancer cell lines in vitro, and may be involved in the transition from the castrate-sensitive to the castrate-resistant state.[59,60] Of further interest, Src is implicated in osteoblast differentiation and osteoclast activation, and inhibitors have demonstrated induced apoptosis of osteoclasts, reduced bone resorption, but enhanced bone-forming activity through osteoblast activity.[61,62] For an excellent overview of Src and its implications in prostate cancer, see the 2007 article by Karim Fizazi in the *Annals of Oncology.*[63]

A phase II study of dasatinib (Sprycel) monotherapy in 47 patients with chemotherapy-naive CRPC reported lack of progression in 43% of patients at week 12 and in 19% at week 24, reductions in uNTx and bone-specific alkaline phosphatase (ALP) levels in a majority of patients, and achievement of a PSA decline of ≥ 50% in three patients.[64-66] Dasatinib and other Src inhibitors are interesting in that this class of pharmaceuticals theoretically has both direct anti-tumor effects (evidenced by lack of progression, regression, and/or PSA declines) and bone-targeted mitigation of the deleterious effects of metastases. Although this phase II study demonstrated both these effects, only changes in bone-turnover markers were reported, not clinical outcomes such as SREs or overall survival. Other studies, however, have shown a positive correlation of these markers with clinical outcomes.

A phase I/II study combining dasatinib with docetaxel in patients with metastatic CRPC showed a PSA response in 41% and an objective tumor response in 57% of patients with measurable disease.[67] One third of patients experienced an improvement of disease on bone scan, and two thirds had stable disease in bone for ≥ 6 weeks. A randomized phase III trial of docetaxel and prednisone with or without dasatinib (NCT00744497) is ongoing, with a primary endpoint of overall survival.[68]

In summary, Src kinase inhibitors offer the potential for direct antitumor activity and bone-targeted therapy, although clinical outcomes with respect to SREs have yet to be reported. This class of drugs has been evaluated as monotherapy in chemotherapy-naive patients and is undergoing further study in combination with docetaxel. While there are other Src inhibitors in development, only saracatinib (previously referred to as AZD0530) is currently being studied in prostate cancer.[69,70] Phase II trials of this drug are currently in the recruitment phase.

**Endothelin-A receptor antagonists**

The endothelin pathway has been implicated in the development and progression of PCa. Endothelins modulate vasomotor tone, nociception, cell proliferation, and angiogenesis; in addition, endothelins bind two receptors, endothelin-A and endothelin-B. Patients with metastatic CRPC have been noted to have elevated levels of endothelin-1 in plasma compared with patients with nonmetastatic disease. Endothelins are involved in their involvement with PCa tumor cells, there is evidence that these endorphins are involved in osteoblastic bone turnover activity.[71,72] Inhibitors of the endothelin receptors have thus been studied clinically in the setting of nonmetastatic and metastatic CRPC.

**Atrasentan.** Atrasentan (Xinlay) is primarily an endothelin-A antagonist. Initial, phase II study data comparing a 10-mg oral daily dose of atrasentan to placebo in 288 patients with asymptomatic, metastatic CRPC found encouraging results: there was a statistically significant longer median time to progression with atrasentan (196 vs 129 days; \( P = .021 \)).[73] Median time to PSA progression was also longer with atrasentan than with placebo (155 vs 71 days; \( P = .002 \)). At 180 days, only 35% of placebo-treated patients were free from progression of disease, but 54% of atrasentan-treated patients were still free from progression. Serum markers (lactate dehydrogenase and alkaline phosphatase) were not significantly different between the two groups. Based on these promising data, phase III trials were conducted in patients with nonmetastatic CRPC and in patients with metastatic CRPC.[74,75] Neither trial demonstrated any difference in time to progression between the atrasentan and placebo groups, but there were significant differences in serum bone turnover markers and PSA levels. In the nonmetastatic CRPC trial, there was a trend towards prevention of progression to skeletal metastasis, but this did not reach significance. Bone
pain was not significantly different between the two groups in the metastatic CRPC trial, but a subset analysis of patients with bone metastases at baseline (59%) suggested a greater delay in time to progression. Thus, it has been suggested that this drug class may provide more benefit in patients with bone disease.[72]

**Zibotentan.** Another endothelin-A receptor antagonist, zibotentan (or ZD4054), has undergone testing in phase I and II studies. A phase II study randomly assigned patients with metastatic CRPC to receive placebo or zibotentan; study investigators found that time to progression was not different between the two groups, but overall survival was significantly different (23.5 months vs 17.3 months; HR, 0.65 [80% CI, 0.49–0.86]; \( P = .052 \)). Final analysis demonstrated that there were fewer new metastases to bone with 10 mg zibotentan than with placebo (treatment ratio, 0.83; 80% CI, 0.70–0.98; \( P = .155 \)), but this was not seen with 15-mg dosing (although the latter cohort did have a slightly higher number of baseline bony metastases).[76]

Currently, there are multiple phase III trials underway for both atrasentan and zibotentan as combination therapy with docetaxel in patients with metastatic CRPC; primary outcomes are progression-free survival and overall survival.[77–79] Some survival advantage with this class of drugs and trends towards increased efficacy in patients with metastatic lesions to bone have been seen; we await the final results of the combination trials for final assessment of these drugs with respect to treatment of bony disease, pain, and progression of disease.

**Antisense therapies**

Clusterin functions as a cytoprotective chaperone protein that is upregulated with therapy-induced cell stress; clusterin has been identified as a potential therapeutic target in CRPC.[80] OGX-011 (Custersin) is complementary to the clusterin mRNA translation initiation site, thereby inhibiting its translation into function product. A randomized controlled trial comparing docetaxel plus prednisone with or without OGX-011 in the treatment of patients with metastatic CRPC demonstrated promising results. Overall survival was 23.8 with OGX-011 vs 16.9 months without OGX-011 (HR, 0.50; 95% CI, 0.29–0.87).[81] A second randomized controlled trial examined OGX-011 in combination with docetaxel or mitoxantrone as second-line therapy in patients with metastatic CRPC after progression on docetaxel therapy.[82] Overall survival was 15.8 months in the docetaxel plus OGX-011 arm vs 11.5 months in the mitoxantrone plus OGX-011 arm, comparing favorably to cabazitaxel. Phase III studies of OGX-011 are underway, with one examining survival as a primary endpoint and another examining pain palliation.[83,84]

**Alpha-particle emitters**

Alpha particles consist of two protons and two neutrons, similar to a helium nucleus. They are highly ionizing and have low penetration depth, affecting only nearby tissues and limiting toxicity. There is currently only one alpha-emitting radionuclide under investigation, radium-223 (\(^{223}\text{Ra}; \text{Alpharadin})

Initial phase I data, published in 2005, included 15 PCa and 10 breast cancer patients.[85] Each patient received a single dose of \(^{223}\text{Ra}\), with the doses ranging in intensity from 46 to 250 kBq/kg. Grade 3 neutropenia and leucopenia occurred in two and three patients, respectively. Ten of the 25 patients experienced transient diarrhea. Nausea and vomiting were more frequently observed in the highest dosage group. Notably, pain relief was reported by 52%, 60%, and 56% of the patients after 7 days, 4 weeks, and 8 weeks, respectively. \(^{223}\text{Ra}\) was noted to clear rapidly from blood and was below 1% of initial level at 24 hours. Excretion was primarily gastrointestinal (GI), accounting for the Gi-related side effects.

Another phase I dose-escalation study involved 10 men with progressive CRPC with more than two bone metastases; the patients were treated in three cohorts, with dose levels of 50, 100, and 200 kBq/kg.[86] Patients received one treatment at the cohort-defined dose, followed by one optional treatment 6 weeks later at 50 kBq/kg. This study demonstrated no dose-related toxicities. \(^{223}\text{Ra}\) accumulated in bone metastases within the first 10 minutes of injection. Three patients suffered grade 3 hematologic toxicities, which were not related to dose level. \(^{223}\text{Ra}\) was well tolerated at doses up to 200 kBq/kg.

Another study examined dosimetry and biodistribution of \(^{223}\text{Ra}\) in six patients with CRPC and bone metastases.[87] Doses of absorbed radiation were calculated for various tissues: red marrow, 0.23 Gy/MBq; and lower large intestine wall, 0.05 Gy/MBq. As decaying alpha particles are released from \(^{223}\text{Ra}\), their short range (< 100 \(\mu\)m) affects only a small volume of red marrow, likely accounting for a favorable safety profile even in patients with extensive skeletal metastatic disease.

Phase II data from a larger cohort of patients were published in *Lancet Oncology* in 2007.[88]
Thirty-three patients were randomly assigned to receive 4 IV injections of $^{223}$Ra (50 kBq/kg), and 31 were randomly assigned to receive placebo. Primary endpoints included changes in bone ALP and time to an SRE. Secondary endpoints consisted of side-effect profile, time to PSA progression, and overall survival. ALP declined 66% relative to baseline in the $^{223}$Ra-treated patients, whereas it increased 9% in the patients who received placebo ($P < .0001$). Hazard ratio for time to SRE was 1.75, but significance was not achieved (95% CI, 0.96-3.19; $P = .065$). Time to PSA progression was 26 weeks for $^{223}$Ra vs 9 weeks for placebo. Overall survival was 65 weeks for the treatment group vs 46 weeks for the control group ($P = .066$), but after adjusting for baseline patient characteristics, this became significant ($P = .020$). The bone-targeted effects were significant, yet there was minimum myelotoxicity (no difference was noted between the two groups).

On the basis of these results, a phase III randomized controlled trial with 922 patients was started. Investigators randomly assigned the patients in a 2:1 ratio to receive $^{223}$Ra or placebo, in addition to standard care. Each patient randomized to $^{223}$Ra received injections every 4 weeks for 6 total doses. The primary endpoint was overall survival. Results have not yet been published, but very recently, investigators announced that the trial was going to halt early after a planned interim analysis.[89] The data safety monitoring board noted a 30% reduction in the odds of dying during follow-up in the $^{223}$Ra treatment arm, and a median increase in overall survival of 3 months. Four percent of patients were noted to have suffered hematologic toxicity (2% grade 3/4), and 8% suffered thrombocytopenia (4% grade 3/4).

**Perspectives**

Cytotoxic therapies such as docetaxel and cabazitaxel have been shown to have proven benefit and potential. They are, however, limited by the development of resistance and systemic toxicities. Treatment with other agents after the development of resistance is not well defined, although some of the other drugs discussed in this review may ultimately be of use for patients with chemotherapy-resistant CRPC. In a future article, we will deal with the important challenges of sequencing the many new therapies for CRPC.

**REFERENCE GUIDE**

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Despite an explosion in the number of agents under investigation for the treatment of CRPC, very few offer direct efficacy against metastatic disease spread to the bone. As stated, bony metastasis
accounts for a great deal of morbidity and mortality. Palliation is an important aspect of treatment, and some interventions have also shown success in mitigating SREs. Systemic chemotherapy is likely to remain the mainstay of treatment for CRPC in the years to come, with therapies such as those discussed here used as adjunctive treatments to achieve specific clinical aims. Endothelin-A receptor antagonists may have some activity against tumor in bone, but single-agent studies do not show any evidence of benefit, and it remains unclear whether endpoints other than those reported might be associated with positive results. Nevertheless, these agents are currently under study in combination with other proven therapies for CPRC in the hope of realizing synergistic outcomes. We await these results. Among agents that specifically target bone, alpha pharmaceuticals offer particular promise for activity and safety in men with bony metastasis. Investigators have finished phase I and II studies, and recently ended phase III study early after the safety monitoring board found a significant increase in overall survival in patients receiving $^{223}$Ra compared with those receiving placebo. In a future article, we hope to review in detail the development and clinical activity of this agent. There are ongoing studies examining $^{223}$Ra in combination with docetaxel. If approved for use, it remains to be seen in which patient population and following which other therapies alpha pharmaceuticals might be most appropriate. Given the plethora of agents now available to clinicians, the choice will likely depend largely on the comfort of the physician with the administration of a given therapy (radiopharmaceuticals require extra safety and training) and on discussion with the patient.

**Conclusions**

For many years, docetaxel chemotherapy was the only treatment that showed a true survival advantage for men with CRPC. Now, entire new classes of drugs aim to treat and target disease, palliate symptomatic pain, and prevent SREs. These represent dramatic new advances in the field of urologic oncology and promise a real therapeutic advantage in the treatment of CRPC and bony metastases. Treating physicians will be faced with significant challenges in determining the sequencing of these new agents.

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