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Bone Targeted Agents: Preventing skeletal complications in prostate cancer

Alicia K. Morgans and Matthew R. Smith

Summary

Prostate cancer is both the most common malignancy and the most common cause of cancer death in men. In the United States, there were approximately 217,730 new prostate cancer diagnoses and more than 32,050 deaths in 2010¹. Skeletal complications occur at various points during the disease course, either due to bone metastases directly, or as an unintended consequence of androgen deprivation therapy (ADT). Up to 90% of men with metastatic castration resistant prostate cancer (CRPC) develop bone metastases^{2,3}. Bone metastases are associated with pathologic fractures, spinal cord compression, and bone pain and can require narcotics or palliative radiation for pain relief. Additionally, ADT results in bone loss and fragility fractures.

This review describes the biology of bone metastases, skeletal morbidity in men with prostate cancer, and recent advances in bone targeted therapies to prevent skeletal complications of prostate cancer.

Keywords

zoledronic acid; denosumab; prostate cancer; bone metastasis; skeletal-related events; Prostate cancer; skeletal complications; bone; side effects of therapy; ADT

Normal Bone Physiology

Healthy bone is perpetually in a state of turnover, striking a delicate balance between bone resorption by osteoclasts and bone formation by osteoblasts. Estrogen plays an important role in the regulation of this balance through estrogen receptors on osteoblasts and osteoclasts⁴. In low estrogen states, the balance favors bone resorption rather than formation. Low estrogen levels is likely one of the most significant contributors to the decline of bone mineral density in hypogonadal states

Additional regulatory signaling occurs via the receptor activator of nuclear factor- κ B ligand (RANKL) system⁵. RANKL, a member of the tumor necrosis factor (TNF) superfamily of proteins, is produced by osteoblasts and bone marrow stromal cells. It binds to RANK receptors on osteoclasts and osteoclast precursors to induce differentiation, activation and survival of osteoclasts. The activation of RANK ultimately causes increased osteoclast activity and bone resorption. The action of osteoprotegerin (OPG), a protein produced by osteoblasts and other stromal tissues, decreases osteoclast activity by OPG binding RANKL, preventing the RANK/RANKL interaction. Relative levels of OPG and RANKL are thought to play a pivotal role in determining the degree to which bone resorption and formation occur⁶.

Pathophysiology of Bone Metastases

Bone lesions in prostate cancer appear osteoblastic radiographically, but both osteoblast and osteoclast activity is upregulated⁷⁻⁹. Osteoclast activity is enhanced by several mechanisms, including marrow stromal and tumor secretion of stimulatory proteins that act on nearby osteoclasts. Stromal cells produce RANKL and macrophage colony-stimulating factor (M-CSF) receptor, both of which stimulate osteoclast differentiation and activation¹⁰. Tumor cells also promote osteoclast activity by producing M-CSF and parathyroid hormone-related protein¹⁰. It has also been proposed that osteoclast activation may be explained almost entirely by the effect of androgen deprivation therapy, one of the most common treatments for recurrent or metastatic prostate cancer¹¹. The mechanism of osteoblast activity promotion is less well defined, but is presumed to be driven by stromal and tumor secretion of osteoblast stimulating factors like insulin-like growth factor, bone-morphogenic proteins, transforming growth factor-beta, fibroblast growth factors and others¹².

Clinical Complications of Bone Metastases

The most common site of metastatic disease in advanced prostate cancer is bone, especially the bones of the axial skeleton, pelvis, and long bones. Spread to bone occurs via hematogenous dissemination. The biology of bone metastases is complex. Multiple factors appear to contribute to the bone tropism in prostate cancer including blood flow in the bone marrow, expression of adhesive molecules on cancer cells that bind them to the bone matrix and stroma, and a rich supply of growth factors in the bone microenvironment¹³⁻¹⁵. There is also a significant amount of reciprocal signaling between osteoblasts, osteoclasts, fibroblasts and other cells of the bone microenvironment and prostate cancer cells through the secretion of cytokines, proteases and growth factors that promote prostate cancer cell survival and growth¹⁶.

Both pathologic fractures directly related to metastatic lesions and treatment-related benign osteoporotic fractures occur commonly in men with prostate cancer. Up to 22% of men with metastatic castrate resistant prostate cancer experience pathologic fractures during the course of their disease due to weakened bone integrity in the area of metastasis¹⁷. Benign osteoporotic fractures occur due to the treatment-related decline of BMD that can result in osteoporosis and increase an individual's risk of fracture^{18,19}. Several large retrospective database analyses of men with non-metastatic prostate cancer demonstrated that men treated with ADT have a significantly higher rate of fracture than those who were not, and the risk increases over time as BMD falls^{20,21}.

Bone metastases are also associated with the development of additional skeletal complications. Both pain and weakness can develop from bone or nerve involvement with metastases. Hypocalcemia and subsequent secondary hyperparathyroidism occur due to increased osteoblast activity in metastatic deposits.

Treatment Related Osteoporosis

Androgen deprivation therapy (ADT), via bilateral orchiectomies or through administration of gonadotropin releasing hormone (GnRH) agonists or antagonists, is the cornerstone of systemic treatment for prostate cancer. The goal of ADT is to dramatically lower serum testosterone, typically <20 ng/dL, or <5% of baseline values. Because of peripheral aromatization of testosterone to estradiol, reducing serum testosterone causes estradiol levels to fall. Estradiol levels decline to <20% of baseline values, reaching levels as low as or lower than those of post-menopausal women.

ADT is widely used, both in subgroups of men with prostate cancer who clearly have improved overall survival with ADT, and in those in whom a survival benefit has not been demonstrated. One group that appears to benefit from treatment with ADT is men with metastatic disease who have an improved overall survival and quality of life with treatment. Men undergoing treatment with radiation for high risk localized disease or locally advanced prostate cancer experience prolonged survival with the addition of ADT²². Finally, there is evidence that men who have positive lymph nodes after radical prostatectomy have improved overall survival when treated with ADT²³. Although there is no evidence of improved overall survival in men with a PSA-only relapse, this population is frequently treated with ADT alone or in combination with salvage radiation²².

The major causes of osteoporosis in men are use of steroids, alcohol use, or hypogonadism²⁴. The intended therapeutic effects of ADT is marked hypogonadism. Consistent with the important role of gonadal steroids in normal bone metabolism in men, ADT decreases BMD and is associated with greater fracture risk. Within six to nine months of initiating ADT, BMD falls²⁵⁻²⁷. BMD continues to decline during treatment at a rate of 2-3% per year²⁵⁻²⁸. This is substantially faster than typical age related decline in men of 0.5%-1%.

ADT is also associated with an increased fracture rate^{20,21}. Within five years of initiating therapy with ADT, the incidence of fracture approaches 20%²⁰. Several large retrospective analyses found that men treated with ADT experience a 21%-45% relative increase in fracture risk as compared to men not treated with ADT^{20,21,29}. Additionally, a SEER Medicare analysis of more than 50,000 men with prostate cancer found a fracture rate of 19.4% in men treated with ADT, while the rate of fracture in men not undergoing treatment was 12.6% ($P<0.001$)²⁰. A second analysis of Medicare data from the same year included 4,000 men with nonmetastatic prostate cancer and reported a relative risk of fracture of 1.21 among men treated with ADT as compared to those who were not (95% CI, 1.14-1.29, $P<0.01$)²¹.

Mechanisms of Treatment-Related Bone Loss

ADT decreases BMD through several mechanisms. Both testosterone and estrogen are important for maintaining normal bone homeostasis, and ADT causes a significant decline in both testosterone and estrogen. When serum testosterone is low, less testosterone is available to undergo peripheral aromatization to estradiol. Low estrogen states are associated with increased bone resorption. In healthy men, studies demonstrate a decline in bone mineral density when estradiol levels are low, and an inverse relationship between fracture risk and estradiol levels³⁰⁻³².

ADT also affects the rate of bone turnover and skeletal sensitivity to parathyroid hormone. Serum markers of osteoblast activity, like bone specific alkaline phosphatase and osteocalcin, and markers of osteoclast activity, such as N-telopeptide, increase in men treated with ADT²⁷. These markers generally increase within 6-12 weeks of initiating therapy with ADT, and plateau approximately 6 months after starting therapy. ADT also increases skeletal sensitivity to parathyroid hormone³³.

Osteoclast Targeted Therapy

Two osteoclast-targeted therapies have been studied in men with prostate cancer. Bisphosphonates are used to prevent skeletal related events (SREs) in metastatic castrate resistant prostate cancer. SREs are a group of skeletal complications associated with malignancy. The term typically encompasses the following outcomes: pathologic fractures, cord compression, and the use of surgery or radiation to treat unstable or painful metastatic

lesions in bone. Some studies also include the development of hyper- or hypocalcemia in the definition. Denosumab, a fully humanized monoclonal antibody targeting RANKL, has been approved to prevent SREs in metastatic solid tumors, including castrate resistant prostate cancer, and to increase BMD in men at risk for ADT-associated bone loss.

Bisphosphonates

Bisphosphonates prevent bone resorption through several mechanisms, including decreased osteoclast differentiation and survival and increased osteoblast survival³⁴. Bisphosphonate molecules are structurally similar to native pyrophosphate molecules that normally adhere to hydroxyapatite crystal binding sites. The molecules attach to binding sites located in areas of bone resorption, reducing osteoclast activity by preventing their adherence to the bone surface and the formation of the ruffled border. Bisphosphonates impair osteoclast progenitor differentiation and survival via their effects on osteoblasts³⁴.

Bisphosphonates vary by the R2 group attached to their common structural backbone. The R2 group determines the potency of the molecule, with nitrogen-containing bisphosphonates like pamidronate, alendronate and zoledronic acid being significantly more potent than simple bisphosphonates like clodronate and etidronate that are non-nitrogenous. Among the nitrogen-containing bisphosphonates, those that contain secondary or tertiary amino groups, such as zoledronic acid, are significantly more potent than other compounds³⁵. Zoledronic acid is estimated to be at least 100 times more potent than pamidronate and more than 1000 times as potent as etidronate in vitro³⁵.

Several bisphosphonates are currently used in patients with cancer. Indications include hypercalcemia, low bone mineral density, and metastatic lesions in bone. As early as the 1990s, evidence demonstrated that pamidronate decreased the risk of skeletal complications in individuals with metastatic breast cancer and multiple myeloma^{36, 37}. Pamidronate was subsequently approved for use in these populations in 1995. Zoledronic acid was approved to prevent skeletal complications in multiple myeloma and in any solid tumor with bone metastases in 2002^{17, 38, 39}. The study that specifically led to its approval in metastatic prostate cancer, Zometa 039, demonstrated a reduction in SRE as compared with placebo¹⁷.

Denosumab

As described above, bone exists in state of continuous remodeling, striking a balance between osteoclast resorption and osteoblast formation of new bone. The RANKL/RANK system plays a key role in achieving this balance. Currently, the only available therapy that targets this system is denosumab, a fully human monoclonal antibody directed at RANKL. The drug mimics the action of OPG by binding RANKL and reducing osteoclast action. It has a half-life of more than 30 days, does not accumulate in bone like bisphosphonates, and can be used in patients with renal insufficiency⁴⁰. Similar to bisphosphonates, treatment with denosumab carries a small risk of developing osteonecrosis of the jaw⁴¹.

Denosumab has been studied to prevent the development of osteoporosis and reduce the risk of fracture in postmenopausal women^{42,43}. In the fracture prevention trial, 7868 postmenopausal women with osteoporosis were randomized to receive placebo or twice yearly denosumab. Women in the denosumab group developed fewer new vertebral fractures, nonvertebral fractures, and hip fractures than those in the placebo group during the 36 month follow up period (relative decreased risk of vertebral fractures 68%, nonvertebral fractures 20%, and hip fractures 40%)⁴⁴. Denosumab was approved by the Food and Drug Administration to treat postmenopausal women with osteoporosis based on this study.

Denosumab was also studied in women with breast cancer who were being treated with aromatase inhibitors⁴⁵. Aromatase inhibitors are associated with a decline in BMD in

women due to the inhibition of peripheral tissue estrogen production. A recent study demonstrated that denosumab prevents the loss of BMD at the lumbar spine in women with breast cancer being treated with aromatase inhibitors as compared to placebo (BMD increased by 5.5% and 7.6% at 12 and 24 months, respectively ($P < .0001$ at both time points)).

Clinical Uses of Osteoclast-Targeted Therapies in Prostate Cancer

Prevention of Therapy-Related Fragility Fractures

Several medications have been evaluated for prevention of fragility fractures, the most clinically relevant endpoint in this population (Table 1). Denosumab, the fully human monoclonal antibody against RANKL, has been approved to prevent treatment-related fragility fractures in men treated with ADT⁴⁶. Toremifene, a selective estrogen receptor modulator (SERM) has been studied in this setting, but has not been approved for use due to an unacceptable risk-benefit ratio⁴⁷. Multiple bisphosphonates, including alendronate, pamidronate, zoledronic acid, and neridronate, have been evaluated to prevent a decline in bone mineral density, but those studies were not powered to evaluate fracture prevention^{18,48-52}.

The National Comprehensive Cancer Network (NCCN) and National Osteoporosis Foundation (NOF) created guidelines for the treatment of secondary osteoporosis associated with ADT and fracture prevention. These guidelines suggest that all men being treated with ADT over 50 years old should be treated with calcium (1200 mg per day) and vitamin D (1000 IU per day). They also recommend additional pharmacologic therapy for fracture prevention for any individual with a 10 year probability of hip fracture $\geq 3\%$ or a 20 year probability of major osteoporotic fracture $\geq 20\%$.

An individual's 10 year probability of fracture depends on multiple factors besides bone mineral density (BMD)^{53,54}. BMD is routinely used as a surrogate endpoint for fracture in clinical trials, but most fractures occur in men whose BMD is not in the osteoporotic range. A man's risk of fracture increases by approximately 30 fold between the ages of 50 and 90, and the decline of bone mineral density with age only accounts for a 4-fold increase in risk of fracture⁵³. To address this, the NOF recommends using the World Health Organization (WHO)/Fracture Risk Assessment (FRAX) computer based tool to calculate the 10 year probability of hip or major osteoporotic fracture⁵⁵. This population-specific assessment is based on various easily obtained clinical factors in addition to BMD, and it can be calculated without BMD data if that is not available.

In clinical practice, more individuals meet criteria for pharmacologic management of therapy-related osteoporosis than would be expected based on the WHO definition of osteoporosis alone (T-score of < -2.5 alone). One recent study applied FRAX to 363 patients with non-metastatic prostate cancer being treated with ADT in an academic practice⁵⁶. In that cohort, 51.2% met criteria for pharmacologic treatment. Age played a major role in the risk stratification, with 3.3% of men < 70 years old and 99.8% of men ≥ 80 years old meeting criteria⁵⁶.

Denosumab HALT 138—Denosumab was studied in a phase 3, multicenter, double-blind, randomized controlled trial evaluating whether it could prevent osteoporosis and reduce the rate of fracture in men treated with ADT (Table 1)⁴⁶. Men in the study were treated with a GnRH agonist for nonmetastatic hormone-sensitive prostate cancer, and were at high risk of fracture based on low baseline BMD, age > 70 years, or previous fragility fracture. A total of 1468 subjects were randomized to receive denosumab or placebo subcutaneously every 6 months, and bone mineral density was evaluated at 24 and 36

months. The primary endpoint in the study was the change in lumbar spine BMD, and incidence of new vertebral fracture was included as a secondary endpoint.

The trial found that there was both an increase in BMD and a decrease in the rate of clinical fracture in men treated with denosumab as compared to placebo⁴⁶. At 24 months, there was a 5.6% increase in lumbar spine BMD in the group treated with denosumab as compared with a 1.0% decrease in BMD in the placebo group ($P<0.001$). Significant differences in BMD were evident in some patients as soon as one month after treatment. At 36 months the denosumab group had significantly fewer vertebral fractures, with an incidence of 1.5% in the denosumab group and 3.9% in the placebo group (relative risk 0.38, $P=0.006$).

Subgroup analyses revealed that denosumab improved BMD at all skeletal sites in all subgroups⁵⁷. The men with the most pronounced improvement in BMD were those with the highest markers of bone turnover (serum C-telopeptide and tartrate-resistant alkaline phosphatase). Adverse events were not significantly different between the two groups.

Based on the results of this trial, denosumab was recently approved by the FDA for fracture prevention in men receiving ADT.

Toremifene protocol G300203—Selective estrogen receptor modulators (SERMs), including raloxifene and toremifene, have been studied to prevent therapy-related fragility fractures in men treated with ADT, but are not approved for use in men with prostate cancer^{47, 58}.

Toremifene was evaluated in a recently reported multicenter, international phase III study of 1,294 men with non-metastatic prostate cancer who were being treated with ADT (Table 1)⁴⁷. Men were at high risk of fracture due to low BMD or age >70 years. Subjects were randomized to receive oral toremifene daily or placebo, and they were followed for two years. The primary endpoint in the study was development of new vertebral fractures, and BMD was assessed as a secondary endpoint. This study revealed that toremifene was associated with a relative risk reduction of 50% in the incidence of new vertebral fractures, with a fracture incidence of 2.5% in the toremifene group versus 4.9% in the placebo group (95% CI -1.5 to 75.0, $p=0.05$). Notably, toremifene was also associated with a higher rate of venous thromboembolic events than placebo, and has not been approved for fracture prevention in men receiving ADT (2.6% vs. 1.1%, respectively)⁴⁷.

Metastatic Castration-Resistant Prostate Cancer

There have been three contemporary randomized controlled trials of bisphosphonates to prevent skeletal complications in patients with castrate resistant prostate cancer and bone metastases (Table 2). Zoledronic acid is the only bisphosphonate approved to prevent skeletal related events in men with metastatic prostate cancer. In a recent global randomized controlled trial, denosumab was superior to zoledronic acid for prevention of SREs in men with castrate resistant prostate cancer and bone metastases and is approved to prevent SREs in this setting.

Zometa 039

The Zometa 039 trial provided the basis for the FDA approval of zoledronic acid for the prevention of SRE in CRPC with bone metastases. The study included 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases (Table 2)¹⁷. Subjects were randomized to receive 4 mg IV zoledronic acid, 8 mg IV zoledronic acid, or placebo every 3 weeks for 15 months, in addition to treatment with ADT and any other therapy provided by their treating physician. The primary endpoint was the proportion of patients having at least

one SRE, defined as pathologic bone fracture, spinal cord compression, surgery to bone, radiation to bone, or change in antineoplastic therapy to treat bone pain.

Because of an unacceptable number of grade 3 elevations in creatinine in the 8 mg zoledronic acid arm, changes were made in zoledronic acid dosing and administration. All participants in the 8 mg zoledronic acid group were switched to 4 mg dosing for the remainder of the trial, and creatinine was assessed prior to each dose. In addition, the infusion period of zoledronic acid was lengthened from 5 minutes to 15 minutes. Following these changes, the frequency of adverse renal events was similar between the zoledronic acid and placebo arms. At the conclusion of the study, only the 4 mg zoledronic acid and placebo data were compared in the primary efficacy analysis.

At the study's conclusion, a significantly smaller proportion of men in the 4 mg zoledronic acid arm experienced SRE than in the placebo arm (33.2% versus 44.2%; $P = .021$)⁵⁹. The median time to first SRE was shorter in the placebo arm than in the 4 mg zoledronic acid arm (321 day versus not reached; $P = 0.009$). Urinary markers of bone resorption were lower in the zoledronic acid arms than the placebo arm ($P = 0.011$ for both doses of zoledronic acid versus placebo). There was no significant difference in overall survival between the zoledronic acid and placebo groups.

CGP 032 and INT 05

CGP 032 and *INT 05* evaluated the effectiveness of IV pamidronate for pain reduction in men with CRPC and symptomatic bone metastases (Table 2)⁶⁰. Both trials were similarly designed multicenter, randomized, placebo-controlled trials, which allowed their results to be pooled and reported together. Between the two trials, 350 men with CRPC and painful bone metastases were randomized to receive pamidronate (90 mg IV) or placebo every 3 weeks for 27 weeks. The primary endpoint was change from baseline self-reported pain score, and secondary endpoints included analgesic use and the proportion of patients with an SRE (defined as pathologic fracture, radiation or surgery to bone, spinal cord compression, or hypercalcemia). Serum and urinary markers of bone turnover were also assessed.

At the conclusion of the studies, the pooled results were unable to demonstrate a difference between the pamidronate and placebo arms in self-reported pain score, analgesic use, proportion of patients with an SRE, or overall survival⁶⁰. Urinary markers of bone turnover were significantly lower in the pamidronate group.

There are several possible reasons for the lack of apparent efficacy of pamidronate in these studies while zoledronic acid demonstrated efficacy in SRE prevention. First, pamidronate is significantly less potent than zoledronic acid, being approximately 100 times less potent than zoledronic acid in vitro. In vivo pamidronate decreases urinary N-telopeptide, a marker of bone turnover, by approximately 50%, while zoledronic acid decreases biomarkers of osteoclast activity by 70-80%¹⁷. Additional reasons for the difference in outcome between these studies and the *Zometa 039* trial include a patient population with more advanced disease (symptomatic bone metastases versus asymptomatic metastases) and less precise study endpoints.

NCIC CTG PR.6

Clodronate was evaluated in National Cancer Institute of Canada Clinical Trials Group PR.6 study to determine its ability to palliate bone pain in men with CRPC and symptomatic bone metastases (Table 2)⁶¹. The study included 209 men treated with mitoxantrone (12 mg/m² IV every three weeks) and prednisone (5 mg PO twice daily) who were randomized to receive clodronate 1,500 mg IV or placebo every three weeks. The primary endpoint was palliative response determined by a reduction in patient reported pain intensity index to zero

or by 2 points, or a decrease in analgesic use by 50%, without an increase in either. Secondary endpoints included duration of response, symptomatic disease progression-free survival, and overall quality of life.

Clodronate did not increase the palliative response of men with CRPC and symptomatic metastatic bone lesions when compared to placebo (46% response versus 39% response in clodronate and placebo, respectively; $P = .54$). When compared to placebo, clodronate was equivalent in its effect on overall quality of life, overall survival, duration of response, and symptomatic disease progression-free survival. A subgroup analysis indicated that clodronate may provide some benefit as compared to placebo for pain palliation in men with severe pain, but the authors note that additional evidence will be necessary to confirm this conclusion.

Denosumab Protocol 20050103

Denosumab was compared to zoledronic acid in an international, phase III, randomized, controlled trial to evaluate its ability to prevent SRE in men with CRPC (Table 2)⁶². The trial included 1901 men who were randomized to receive denosumab (120 mg subcutaneously every 4 weeks) or zoledronic acid (4 mg IV every 4 weeks). The primary endpoint was time to first on-study SRE, defined as pathologic fracture, radiation to bone, surgery to bone, or spinal cord compression. The study aimed to demonstrate non-inferiority of denosumab as compared to zoledronic acid. Secondary objectives were to assess for superiority of denosumab and compare drug safety profiles.

After a median follow-up of 12.2 months for men treated with denosumab and 11.2 months for men receiving zoledronic acid, denosumab prolonged the median time to first on-study SRE by 3.6 months as compared to zoledronic acid (HR, 0.82, 95% CI, 0.71-0.95; $P = 0.0002$ for non-inferiority; $P = 0.008$ for superiority)⁶². Overall survival was similar between the denosumab and zoledronic acid groups. The safety profiles were also similar. Compared to zoledronic acid, denosumab was associated with similar rates of osteonecrosis of the jaw (1% versus 2%; $P = 0.09$) and higher rates of hypocalcemia (6% versus 13%; $P < 0.001$). Denosumab was approved by the FDA for use in individuals with metastatic solid tumors, including prostate cancer, for the prevention of SREs.

Metastatic Castration-Sensitive Prostate Cancer

Bisphosphonates

Several studies have evaluated the use of bisphosphonates in men with hormonally sensitive metastatic prostate cancer. Initial data from a one study evaluating clodronate for the prevention of symptomatic skeletal disease progression or prostate cancer death was negative. Long-term data from that study demonstrating an improved overall survival with clodronate has not yet been incorporated into widespread clinical practice. A second study in this population, CALGB/CTSU 90202, is investigating the use of zoledronic acid in this setting and is ongoing.

MRC PR05

The Medical Research Council PR05 study evaluated clodronate in men with metastatic prostate cancer who were initiating or continued to be responsive to initial treatment with ADT (Table 2). In the study, 311 men were randomized to clodronate (2080 mg PO daily) or placebo in addition to continuing treatment with primary ADT⁶³. The primary study endpoint was bone progression-free survival defined at time to either symptomatic disease progression or prostate cancer death. Compared to placebo, clodronate did not significantly improve bone progression free survival (HR, 0.79; 95% CI, 0.61-1.02; $P = .066$). Treatment

with clodronate was associated with longer overall survival—a secondary endpoint of the study (8 year OS, 22% vs. 14%; HR, 0.77; 95% CI, 0.60-0.98; $P=0.032$)⁶⁴.

CALGB/CTSU 90202

A second study investigating the use of bisphosphonates in men with hormonally responsive metastatic prostate cancer is the ongoing *CALGB/CTSU 90202* (NCT00079001) trial (Table 2). The study aims to randomize 680 men with castrate-sensitive disease and skeletal metastases to receive zoledronic acid (4 mg IV every 4 weeks) or placebo. Endpoints include SRE and prostate cancer death. Because it is FDA approved for prevention of SRE in metastatic castrate-resistant disease, patients cross over to zoledronic acid when they develop castrate-resistant disease or experience an SRE. This study remains open to enrollment.

Prevention of Bone Metastases

Several osteoclast-targeted therapies have been evaluated to prevent metastases in men with high risk or locally advanced disease. Two bisphosphonates, clodronate and zoledronic acid, were studied in randomized, placebo-controlled trials. In *MRC PR04*, clodronate failed to significantly prolong bone-metastasis free survival. A trial evaluating the ability of zoledronic acid to prolong time to first metastasis, *Zometa 704*, did not reach its accrual goal and was therefore not evaluable. *ZEUS* is an ongoing European randomized, controlled trial evaluating the efficacy of zoledronic acid in metastasis prevention in men with high risk prostate cancer. In contrast, a recently reported randomized, placebo-controlled, phase III trial demonstrated that denosumab prolonged bone-metastasis free survival when compared to placebo.

MRC PR04

Clodronate was evaluated in a randomized, double-blind, placebo-controlled trial for the prevention of symptomatic bone metastases in the Medical Research Council PR04 study (Table 3). The trial enrolled 508 men with locally advanced prostate cancer (T2-T4, N0, N+, or NX, M0) who were considered to be at high risk of developing metastases⁶⁵. Men were randomized to 5 years of treatment with clodronate (2080 mg orally per day) or placebo, and most received treatment of their prostate cancer consistent with standard of care at the time (external beam radiation, external beam radiation and hormonal therapy, or primary hormonal therapy). The primary endpoint was bone metastasis-free survival, a composite endpoint that included development of symptomatic bone metastasis or death from prostate cancer. After median follow-up of 118 months and 148 primary endpoint events, there was no difference in bone metastasis-free survival or overall survival between the two groups. There was a trend towards men in the placebo arm experiencing fewer events than those in the clodronate arm, though this did not reach significance (HR=1.22, 95% CI=0.88 to 1.68; $P=.23$). Excluding PSA level, after 226 events, men in the clodronate arm had shorter time to disease progression than those in the placebo arm (HR = 1.31, 95% CI = 1.01 to 1.70; $P = .041$). Overall survival at 5-years was similar between the two groups at 78%. Despite evidence of a survival advantage in the castrate-sensitive metastatic setting after long-term follow up, there was no difference in overall survival after long-term follow up in this population with locally advanced castrate-sensitive disease⁶⁴.

Zometa 704

Zometa 704 was a randomized controlled trial evaluating the ability of zoledronic acid to prolong time to first metastasis in men with CRPC and a rising PSA but no radiographic evidence of metastatic disease (Table 3)⁶⁶. Men were randomized to receive zoledronic acid

(4 mg IV every 4 weeks) or placebo. The primary endpoint was time to first metastatic bone lesion, and subjects were evaluated by bone scan every four months.

Although planned accrual was 991, the trial was closed after only 398 men had enrolled due to a low event rate. Analysis of the available data found no difference in time to first metastasis between zoledronic acid and placebo, although the low event rate and early study termination precludes reliable conclusions about efficacy of zoledronic acid in this setting.

Zometa European Study (ZEUS)

ZEUS is an ongoing randomized, controlled, open-label study evaluating the ability of zoledronic acid to prevent bone metastases in a high-risk population (Table 3)⁶⁷. Subjects have high-risk localized castrate-sensitive prostate cancer, defined by having one of the following disease characteristics: PSA ≥ 20 ng/mL, lymph-node positive disease, or Gleason score of 8-10. Subjects were randomized to receive zoledronic acid (4 mg IV every 3 months for 48 months) or placebo, and additional treatment was delivered per standard of care. The primary endpoint is the proportion of men who develop at least 1 bone metastasis during a 48 month study period. Target accrual of 1300 men has been met and the study is ongoing.

Denosumab Protocol 20050147

Denosumab has been evaluated for its activity in metastasis prevention in a recently reported international, phase III, double-blind, randomized controlled trial, *Denosumab Protocol 20050147* (Table 3). This study randomized 1,435 men with non-metastatic CRPC at high risk of developing metastatic disease to receive denosumab (120 mg subcutaneously every 4 weeks) or placebo⁶⁸. High risk was defined as PSA ≥ 8.0 μ g/L, PSA doubling time ≤ 10 months, or both. The primary endpoint of the trial was bone-metastasis free survival, which included time to first bone metastasis (symptomatic or asymptomatic) or death from any cause. Overall survival was a secondary endpoint.

Denosumab prolonged median bone-metastasis free survival by 4.2 months as compared to placebo (29.5 months (95% CI, 25.4-33.3) versus 25.2 months (95% CI, 22.2-29.5), respectively)⁶⁸. Additionally, denosumab delayed time to first bone metastasis when compared to placebo (median 33.2 months (95% CI, 29.5-38.0) vs. 29.5 months (95% CI, 22.4-33.1), respectively). Overall survival was equivalent between groups (median overall survival of 43.9 months with denosumab and 44.8 months with placebo (HR, 1.01, 95% CI, 0.85-1.20; $P=0.91$)). Notable adverse events included hypocalcemia and osteonecrosis of the jaw in 2% and 5% of men receiving denosumab, respectively. Hypocalcemia occurred in $<1\%$ of men receiving placebo, and there were no episodes of osteonecrosis of the jaw.

Radioisotopes

Both alpha and beta emitting radioisotopes have been studied for pain palliation in men with prostate cancer and painful bone metastases. Two beta emitting radioisotopes, Strontium-89 and Samarium-153, have been approved for bone metastasis pain palliation in men with prostate cancer. Radium-223, an alpha emitting radioisotope, has also been studied for palliation of bone pain in men with metastatic prostate cancer. In a recently reported international, phase III, randomized, placebo-controlled trial, radium-223 prolonged overall survival in men with CRPC and painful bone metastases.

Strontium-89 and Samarium-153

Strontium-89 and Samarium-153 are beta emitting radioisotopes that have been approved for use in men with CRPC and painful bone metastases. They act by honing to tissues

surrounding osteoblastic lesions to deliver high energy radiation therapy locally. They are especially useful for treating multifocal lesions that are not easily targeted in a single radiation field or for the palliation of tissues that have previously received maximum doses of external beam radiation.

Several clinical trials have evaluated the efficacy of strontium-89 for pain palliation in men with CRPC and bone metastases. A British study included 284 men treated with strontium-89 or conventional focal or hemibody external beam radiation therapy⁷⁹. Pain control was similar between the groups at 3 months, though bone marrow suppression was more common in the strontium-89 group. A phase III, randomized, controlled Canadian trial included 126 men with hormone-resistant prostate cancer and painful bone metastases who were randomized to receive strontium-89 or placebo after initial treatment with focal external beam radiation⁷⁰. Overall survival was similar between the two groups, but men treated with strontium-89 had improved quality-of-life scores and more frequently discontinued pain medications at three months than those treated with placebo. In contrast, a European Organization for Research and Treatment of Cancer (EORTC) study randomized 203 men to receive local field external beam radiation or strontium-89⁷¹. There was no difference between the groups in pain relief, but overall survival was significantly higher in the external beam group (median OS 11 vs. 7 months, $P=0.046$).

Samarium-153 has also been studied in phase III, randomized, placebo-controlled studies in men with prostate cancer. In the first, 118 individuals with bone metastases from various solid tumors were randomized to 0.5 mCi/kg or 1.0 mCi/kg of samarium-153 or placebo⁷². Prostate cancer patients made up 68% of the group. During the first four weeks of the study, the high dose of samarium-153 was associated with significantly less pain than placebo. There was no difference between groups in overall survival. A second study randomized 152 men with CRPC to receive samarium-153 or placebo⁷³. Men receiving samarium-153 had significantly lower analgesic use at three and four weeks during the study.

Complications from beta radioisotopes occur due to the effects of radiation on the tissue surrounding metastatic lesions. The most common adverse effect is myelosuppression, and blood counts should be monitored at least once every two weeks during treatment. Additional complications include severe pain flare in <10% of men, and acute leukemia has rarely been associated with Strontium-89^{74, 75}.

ALSYMPCA

Radium-223 is an alpha emitting radioisotope that is currently being evaluated in the Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, an international, randomized, controlled, phase III study. The trial included 922 men with CRPC and 2 symptomatic bone metastases but no visceral metastases who had received docetaxel or were unfit to receive it⁷⁶. They were randomized to radium-223 (50 kBq/kg) or placebo. The primary endpoint of the study was overall survival, and secondary endpoints included time to first SRE, time to PSA progression, and total alkaline phosphatase normalization.

After 314 events from 809 randomized patients were collected, a planned interim analysis was performed. Because radium-223 was associated with a significant improvement in overall survival as compared to placebo, the trial was closed immediately (median survival 14.0 versus 11.2 months, hazard ratio 0.695, $p=0.002$)⁷⁶. Radium-223 also prolonged time to first SRE (13.6 months versus 8.4 months for radium-223 and placebo, respectively). The most common complications associated with radium-223 versus placebo include anemia (27% versus 27%), bone pain (43% versus 58%), and nausea (34% versus 32%). This medication is not yet approved for use in men with CRPC and symptomatic bone metastases in the United States.

Conclusions

In prostate cancer, both metastatic lesions and the effects of hormonal therapy can have negative effects on the skeletal system. Multiple therapies have been developed to target bone related complications for men at various stages of the disease. Evidence supports the use of osteoclast inhibiting therapies in men treated with ADT to prevent therapy-related fragility fractures. There is also evidence that osteoclast inhibiting therapies are beneficial in preventing SREs in men with CRPC. More recently phase III data demonstrates that using denosumab in men with CRPC can prevent the development of metastases. Finally, radium-223 prolongs overall survival in men with CRPC and skeletal metastases after treatment with docetaxel. The spectrum of bone-targeted therapies for the skeletal complications of prostate cancer continues to evolve, providing numerous novel options in our arsenal against bone complications in this disease.

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Key Points

Skeletal complications from metastases and ADT are common in prostate cancer.
Multiple bone targeted agents are available and being developed for use in this disease.

Table 1

Bone targeted therapies evaluated for the prevention of therapy-related fragility fractures.

Study	N	Study population	Arms	Outcome
Denosumab Halt 138 ⁴⁶	1468	Men with non-metastatic prostate cancer being treated with a GnRH agonist and at high risk of fracture.	Denosumab 60 mg subcutaneously every 6 months vs. placebo for 3 years	Denosumab was associated with a significant increase in BMD ($P<0.001$) and a decrease in the incidence of vertebral fractures (RR 0.38 as compared to placebo, $P=0.006$).
Toremifene protocol G300203 ⁴⁷	1294	Men with non-metastatic prostate cancer being treated with ADT who were at high risk of fracture.	Toremifene 80 mg orally daily vs. placebo	Toremifene was associated with a 50% reduction in the relative risk of new vertebral fracture and an increase in bone mineral density ($P=0.05$). Elevated risk of thromboembolic events in the toremifene arm.

Table 2

Randomized controlled trials of bone targeted therapies in prostate cancer with bone metastases.

Study	N	Study population	Arms	Outcome
Zometa 039 ¹⁷	643	Men with CRPC and symptomatic or minimally symptomatic bone metastases	Zoledronic acid 4 mg intravenously every 3 weeks vs. placebo	Zoledronic acid was associated with significantly fewer SRE (33.2% vs. 44.2%) and a trend towards improved overall survival.
CGP 032/INT 05 ⁶⁰	350	Men with CRPC and symptomatic bone metastases	Pamidronate 90 mg intravenously every 3 weeks or placebo	No difference in self-reported pain score, analgesic use, or SREs.
NCIC CTG PR.6 ⁶¹	209	Men with CRPC and symptomatic bone metastases	Clodronate 1500 mg intravenously every three weeks or placebo	No difference in palliative response, overall quality of life, overall survival, duration of response, or symptomatic disease progression.
Denosumab protocol 20050103 ⁶²	1901	Men with CRPC	Denosumab 120 mg subcutaneously or zoledronic acid 4 mg intravenously every 4 weeks	Denosumab prolonged the median time to first on-study SRE by 3.6 months (met both non-inferior and superiority endpoints). No difference in overall survival or adverse events (including osteonecrosis of the jaw).
MRC PR05 ^{63,64}	311	Men with castration-sensitive prostate cancer with bone metastases	Clodronate 2080 mg orally daily vs. placebo	Trend towards improved progression-free and overall survival with clodronate on initial analysis, and significantly prolonged overall survival at 8-year analysis.
CALGB/CTSU	680 [*]	Men with castration-sensitive prostate cancer with bone metastases	Zoledronic acid 4 mg IV every 4 weeks or placebo	Endpoints are SRE and prostate cancer death. Study is ongoing.

* target accrual

Table 3

Bone targeted therapies evaluated for metastasis prevention in nonmetastatic prostate cancer.

Study	N	Study population	Arms	Outcome
MRC PR04 ⁶⁵	508	Men with locally advanced prostate cancer at high risk of developing metastases.	Clodronate 2080 mg orally daily vs. placebo for 5 years	No difference in bone metastasis-free survival or overall survival.
Zometa 704 ⁶⁶	398	Men with CRPC and rising PSA without radiographic evidence of metastatic disease.	Zoledronic acid 4 mg intravenously every 4 weeks vs. placebo	Poor accrual and low event rate caused early closure of the trial and impairs analysis of study results.
ZEUS ⁶⁷	1300	Men with high-risk localized castrate-sensitive prostate cancer	Zoledronic acid 4 mg intravenously every 3 months or placebo for 48 months	Target accrual complete, data acquisition and analysis ongoing.
Denosumab protocol 20050147 ⁶⁸	1435	Men with non-metastatic CRPC at high risk of developing metastatic disease	Denosumab 120 mg subcutaneously every 4 weeks vs placebo.	Denosumab prolonged median bone-metastasis free survival by 4.2 months as compared to placebo. No difference in overall survival between groups.