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Optimizing bone health and minimizing skeletal morbidity in men with prostate cancer

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Abstract

Maintaining bone health is important in all stages of the management of men with prostate cancer. Patients receiving androgen-deprivation therapy (ADT) are at increased risk of treatment-related osteoporosis and patients with bone metastases are at increased risk of skeletal morbidity related to debilitating skeletal-related events (SREs). Osteoclast-targeted agents have a beneficial impact on bone health in patients with prostate cancer. For patients on ADT at high-risk for fracture, bisphosphonates have been shown to increase bone mineral density (BMD), a surrogate for fracture risk, whereas denosumab (Prolia) has been shown to decrease the risk of osteoporotic fractures, in addition to increasing BMD. For patients with castration-resistant prostate cancer (CRPC) with bone metastases, both zoledronic acid (Zometa) and denosumab (Xgeva) have shown benefit in decreasing the rate of SREs. Currently, no agent is approved for the prevention of bone metastases in high-risk patients. Novel systemic agents including radium-223 (Alpharadin), abiraterone (Zytiga), and enzalutamide (Xtandi) have shown a beneficial effect on the rate of SREs in patients with CRPC with bone metastases by directly impacting tumor growth. Integration of these anti-cancer agents with currently approved osteoclast-targeted agents warrants further investigation.

Keywords

Prostate cancer; Androgen deprivation therapy; Osteoporosis; Bone metastases; Skeletal related events; Bisphosphonate; Zoledronic acid; Denosumab

1. Introduction

Prostate cancer is the most common cancer in men in the United States, with a life time risk of 16%, and the second leading cause of death in this population.^[1] Patients on ADT and/or those with bone metastases are susceptible to skeletal complications. Therefore, optimizing bone health is critical in the management of patients with prostate cancer.

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2. Normal Bone Physiology

Normal bone remodeling is the process by which bone is renewed to maintain strength and mineral homeostasis.^[2] It involves the coordinated actions of osteoclasts, responsible for bone resorption, and osteoblasts, which mediate bone formation (Figure 1).^[2]

The receptor activator of nuclear factor- κ B ligand (RANKL) is a critical cytokine in the remodeling process. RANKL, which is released from osteoblasts and bone marrow stromal cells, binds to RANK receptors on monocyte/macrophage precursor cells, thus promoting osteoclast differentiation, activation, and survival.^[2] Subsequently, mature, multi-nucleated osteoclasts adhere to the bone matrix.^[2] They undergo structural changes to form a resorption lacunae, export acid and lytic enzymes into the lacunae, which leads to hydroxyapatite decalcification and bone degradation.^[2] Osteoprotegerin (OPG), which is secreted from osteoblasts and stromal cells, competitively blocks RANKL binding to its cellular receptor RANK.^[3] The RANKL/RANK/OPG regulatory axis results in tight coupling of the process of bone remodeling. Certain hormones, cytokines, and humoral factors influence bone homeostasis. Pro-resorptive factors include parathyroid hormone (PTH), parathyroid hormone related protein (PTHrP), interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), prostaglandin E2 (PGE2), and vitamin D.^[4]

Osteoblasts arise from osteoprogenitor cells, which are induced to differentiate under the influence of bone morphogenetic proteins (BMP), estrogens, calcitonin, transforming growth factor- β (TGF- β) and platelet derived growth factor (PDGF).^[4] The Wnt signaling pathway and runt-related transcription factor 2 (RUNX2) are critical for the initiation of osteoblast differentiation.^[5] Mature osteoblasts form the connective tissue matrix which mineralizes to become bone.^[4] Thus, the coupling of osteoclast and osteoblast function maintains bone homeostasis.

3. Treatment-related osteoporosis

ADT is the mainstay of systemic treatment for prostate cancer. The intended therapeutic effect of ADT is severe hypogonadism, a common cause of osteoporosis in men.^[6] Based on retrospective Surveillance, Epidemiology, and End Results (SEER)/Medicare claims data, in men diagnosed with prostate between 2000–2002 approximately 45% were exposed to ADT at some point after their diagnosis.^[7] Additionally, the prevalence of ADT is increasing in the US.^[8]

BMD, a surrogate for fracture risk, decreases in men receiving ADT. A rapid loss of BMD occurs within the first 12 months of therapy.^[9–11] Based on a review of data from clinical trials and retrospective studies, rates of bone loss in the lumbar spine ranged from 2–8% and from 1.8–6.5% in the femoral neck during the initial 12 months of ADT.^[12] Typically, men 50 years and older not receiving ADT have BMD lose at a rate of 0.5% per year.^[13] BMD continues to decline with ADT treatment beyond 12 months.^[9, 10, 14]

In addition to decreased BMD, ADT use in men with no bone metastases is associated with an increased risk of clinical osteoporosis-related bone fractures. In a SEER/Medicare claims study of over 50,000 men diagnosed with prostate cancer, of men surviving at least 5 years

after diagnosis, men who received ADT had a significantly higher fracture rate compared to men not receiving ADT (19.4% versus 12.6%; $p < 0.001$).^[15] The risk of fracture increased with longer duration of therapy. This study included patients with both metastatic and non-metastatic disease. In another Medicare claims study of over 11,000 patients, men with non-metastatic prostate cancer receiving gonadotropin-releasing hormone (GnRH) agonist therapy were more likely to develop fractures than a control group of men with non-metastatic prostate cancer not receiving GnRH-agonist treatment (relative risk (RR) 1.21; 95% confidence interval (CI) 1.14–1.29; $p < 0.001$).^[16] Patients receiving less than 1 year of therapy were not at increased fracture risk. Based on retrospective data, there is evidence to suggest that skeletal fracture is an independent negative predictor of survival in patients with prostate cancer (both non-metastatic and metastatic).^[17]

a. Pathophysiology of treatment-related osteoporosis

Testosterone and estrogen are essential in regulating bone integrity in men. The direct effect of estrogen on osteocytes, osteoclasts, and osteoblasts leads to inhibition of bone remodeling, decreased bone resorption, and maintenance of bone formation, respectively.^[18] In a study examining the relative contributions of testosterone versus estrogen towards regulating bone metabolism in men, estrogen accounted for 70% of the total effect of sex steroids on bone resorption in older men.^[19] Based on results from a prospective study, older men with low estradiol were at greater risk for low BMD and increased fracture.^[20]

Given that testosterone undergoes peripheral aromatization to form estradiol, men treated with ADT also have low estrogen states. In a prospective study of men initiating ADT for non-metastatic prostate cancer, there was a 73% decrease in serum estradiol from baseline pre-treatment levels after 48 weeks of treatment.^[21] Low estrogen states are associated with an imbalance between bone resorption and formation, resulting in decreased BMD and increased risk of fracture.^[22–24]

4. Bone metastases in prostate cancer

The skeleton is the most frequent site of metastases in advanced prostate cancer, with estimates of involvement between 80–90% in CRPC.^[25] The most common sites of involvement include the vertebral column, pelvis, ribs, long bones, and skull. Though prostate cancer causes radiographically dense osteoblastic lesions, the woven bone produced by osteoblasts is structurally weak.^[26] Pain is a common symptom associated with the presence of bone metastases. Additionally, patients are at risk of SREs including pathologic fractures, spinal cord compression, need for skeletal radiation, need for surgery to the bone and in some cases hypercalcemia. The rate of SREs in patients with bone metastases and castration resistance ranges from 40–50%.^[27, 28]

a. Pathophysiology of bone metastases

Bone metastases in prostate cancer promote increased osteoblast and osteoclast activity, as made evident by increased biochemical markers of bone turnover.^[29] Interactions between tumor cells and the bone microenvironment result in a vicious cycle of bone destruction and aggressive tumor growth (Figure 2).^[30] Production of interleukins, prostaglandins, and

PTHrH by tumor cells stimulates osteolysis, leading to the release of factors and cytokines derived from the bone matrix. These factors, including TGF- β and PDGF, induce tumor cell proliferation leading to propagation of the vicious cycle of tumor growth and bone destruction.^[30]

5. Osteoclast-targeted therapies

a. Bisphosphonates

Bisphosphonates are stable analogues of a naturally occurring inorganic pyrophosphate (Figure 3). Bisphosphonates have two additional side-chains (R_1 and R_2) which are not present on pyrophosphate. In general, a hydroxyl substitution at R_1 enhances the affinity of bisphosphonates for calcium, while the presence of a nitrogen atom in R_2 enhances the potency of the compound and determines the mechanism of action.^[31] Table 1 highlights the potency of available bisphosphonates based on *in vitro* assays.^[32]

Bisphosphonates bind to hydroxyapatite crystals on exposed bone. They are released in the acidic environment of the resorption lacunae and are taken up by osteoclasts via endocytosis.^[33] Non-nitrogen containing bisphosphonates incorporate into ATP and induce osteoclast apoptosis.^[33] Nitrogen-containing bisphosphonates induce changes in the cytoskeleton of osteoclasts, including loss of the ruffled border, leading to osteoclast inactivation and apoptosis.^[34] This action is mainly the result of inhibition of farnesyl pyrophosphate synthase, an enzyme in the mevalonate pathway, which plays a key role in cholesterol biosynthesis.^[34] In addition to their inhibitory effect on osteoclasts, bisphosphonates appear to have a beneficial effect on osteoblasts.^[35]

Bisphosphonates have poor oral bioavailability, with absorption of only about 1% of an oral dose (Table 2).^[32] Approximately 50% of the absorbed bisphosphonate is rapidly cleared by the kidney, with a half-life of approximately 1 hour, and the remaining 50% is taken up by bone, and may persist there for years.^[32]

Therapy with bisphosphonates is associated with adverse side effects including hypocalcemia, renal impairment, osteonecrosis of the jaw (ONJ), and acute phase reactions.^[36] Bisphosphonates with greater potency and those administered intravenously have a greater potential for adverse events.^[36] Bisphosphonates require dose modification for renal impairment and are not recommended for patients with a creatinine clearance < 30 mL/minute, given risk of hypocalcemia and worsening renal failure. ONJ is a well recognized complication of bisphosphonate treatment. In patients with bone metastases receiving higher doses of intravenous therapy, the incidence is approximately 1–12%.^[37] Currently, the Southwest Oncology Group (SWOG) is investigating the incidence, risk factors, and outcomes associated with ONJ in a prospective trial seeking to enroll a total of 7,200 patients.^[38] Risk factors for the development of ONJ include head and neck radiotherapy, periodontal disease, and dental extractions.^[37] Lastly, about 30% of patients treated with intravenous zoledronic acid are at risk of an acute phase reaction, associated with fevers, myalgias, and nausea which can last longer than 24 hours, but diminishes in duration and intensity with subsequent dosing.^[39]

b. Receptor activator of nuclear factor- κ B ligand inhibitors

Denosumab is a fully human monoclonal antibody administered subcutaneously that has high affinity and specificity for RANKL. It mimics the action of OPG by binding RANKL and reducing the activity of osteoclasts. Unlike bisphosphonates, denosumab does not accumulate in bone and has a longer circulatory half-life (greater than 25 days) (Table 2).^[40] While there are no recommendations for dose adjustment for renal insufficiency, patients with severe renal insufficiency are more prone to hypocalcemia.^[41] Additionally, use of monthly denosumab is not advised when creatinine clearance is < 30 mL/minute, given limited studies in this patient population.

6. Management of treatment-related osteoporosis

a. Defining osteoporosis

The definition and diagnosis of osteoporosis in men relies, at least in part, on female standards.^[43] The World Health Organization (WHO) recommends using the same classification of BMD to define osteoporosis in men, age 50 and older, as in women:^[44]

- Normal is defined as a T-score greater than -1.0.
- Osteopenia is defined as a T-score between -1.0 and -2.5.
- Osteoporosis is defined as a T-score of less or equal to -2.5.

The T-score is reported as the number of standard deviations (SD) that a patient's BMD value is above or below the reference value for a healthy 30 year-old adult. Fracture risk increases approximately two-fold for every SD decrease in BMD.^[45]

b. Who to consider for screening and treatment?

The National Comprehensive Cancer Network (NCCN) guidelines recommend screening and treatment of osteoporosis in men with prostate cancer according to the National Osteoporosis Foundation (NOF) guidelines for the general population (Table 3). In the past, BMD was the primary factor utilized to assess fracture risk despite that most fractures occurred in men with BMD measurements not in the osteoporotic range.^[46] Given that there was a need for more sensitive risk determination, in 2008 the WHO introduced the Fracture Risk Assessment Tool (FRAX), which estimates the 10-year probability of hip fracture and major osteoporotic fracture for untreated patients between ages 40 and 90 years using clinical risk factors for fracture and femoral neck BMD if available (www.shef.ac.uk/FRAX/). The FRAX algorithm is integrated into the NOF recommendations for treatment. Application of the NOF treatment guidelines to men in the Osteoporotic Fractures in Men Study (MrOS) estimated that 34% of United States white men aged 65 years and older and 49% of men aged 75 years and older would be recommended for treatment.^[47] In a study of 363 men receiving ADT for prostate cancer, the FRAX algorithm without BMD assessment estimated that 51.2% of men met criteria for pharmacologic intervention.^[48] The FRAX algorithm with BMD assessment estimated that 15% of men met criteria for pharmacologic intervention. Though the FRAX algorithm uses epidemiological data from the general population, it is still a reasonable strategy to determine fracture risk in men receiving ADT for prostate cancer. To monitor effectiveness of treatment, the NOF recommends baseline

BMD assessment with repeat testing every 2 years, recognizing that more frequent testing may be warranted in certain clinical situations.

c. Pharmacologic interventions for treatment-related osteoporosis

Several agents including bisphosphonates, RANKL inhibitors, and selective estrogen receptor modulators (SERMs) have shown benefit in the management of treatment-related osteoporosis (Table 4). The efficacy of bisphosphonates has been demonstrated in small studies which showed improvement in BMD, however these studies were not powered to assess fracture risk. Denosumab and toremifene have both been evaluated in phase III trials and showed improved BMD and decreased fracture risk. Despite efficacy of these treatments, the optimal agent, schedule, and duration of therapy remain in question.

i. Bisphosphonates—Though multiple bisphosphonates including neridronate (Nerixia), alendronate (Fosamax), pamidronate (Aredia), and zoledronic acid have been shown to decrease bone turnover and improve BMD in men receiving ADT, none have demonstrated statistically significant improvement in the rates of fragility fractures.^[10, 21, 49–53] These were smaller studies designed to primarily evaluate BMD as a surrogate endpoint. In a meta-analysis including 2,634 men with prostate cancer (including both non-metastatic and metastatic disease), treatment with bisphosphonate therapy had a substantial effect in preventing fractures (RR 0.80; $p=0.005$) and osteoporosis (RR 0.39; $p<0.00001$).^[54] Given limited clinical data in men with ADT-associated bone loss, there still exists significant controversy regarding choice of agent, dose, and schedule. Compared to what is typically used for the prevention of SREs in patients with metastatic disease, dosing is appreciably less for the management of treatment-related osteoporosis.^[55]

ii. Receptor activator of nuclear factor- κ B ligand inhibitors—The Denosumab HALT (Hormone Ablation Bone Loss Trial) 138 study, a multi-center, double-blinded, randomized, placebo-controlled trial, enrolled 1,468 men receiving ADT at increased risk of fracture given age ≥ 70 years, low BMD defined as a T score < -1 , or a history of an osteoporotic fracture.^[56] Patients were randomly assigned to treatment with denosumab 60 mg subcutaneously every 6 months for 24 months or placebo. The primary endpoint was percent change in BMD at the lumbar spine at 24 months. A secondary endpoint included incidence of new vertebral fractures. The study demonstrated statistically significant increased BMD at the lumbar spine (6.7% difference between groups), total hip (4.8% difference between groups), femoral neck (3.9% difference between groups), and distal third of the radius (5.5% difference between groups) at 24 months. Additionally, patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5% versus 3.9%; $p=0.006$). The rates of adverse events were similar between the 2 groups. There was one person with hypocalcemia in the treatment arm and zero in the placebo arm. There were no documented cases of ONJ in either group.

iii. Selective estrogen receptor modulators—SERMs have shown benefit in men treated with ADT for prostate cancer secondary to their agonist activity at the estrogen receptor in bone.^[57, 58] In a phase III, international, double-blinded, randomized, placebo-controlled trial, 1,284 men with non-metastatic prostate cancer treated with ADT were

randomized to toremifene (Fareston) or placebo for 2 years.^[58] Patients were at high-risk for fracture given age ≥ 70 years or osteopenia. The primary endpoint was incidence of new vertebral fractures. Men treated with toremifene had significantly fewer new vertebral fractures compared to placebo (2.5% versus 4.9%; RR 0.50; p=0.05). In addition, toremifene significantly increased BMD at the lumbar spine, hip, and femoral neck compared to placebo (p<0.0001). Treatment with toremifene was associated with an increased rate of venous thromboembolic events compared to placebo (2.6% versus 1.1%, respectively).

d. Calcium and vitamin D supplementation

Providing adequate calcium and vitamin D is recommended by the NOF. A meta-analysis of 11 trials, mostly in post-menopausal women, comparing calcium (500 to 1200 mg daily) plus vitamin D (300 to 1100 units daily) with placebo showed that combined supplementation reduced the risk of total fractures (RR 0.88; 95% CI 0.78–0.99).^[59]

The NOF recommends at least 1200 mg daily of calcium for those older than 50 years. Calcium supplements are available in two formulations including calcium carbonate, which requires gastric acid for optimal absorption, and calcium citrate, which does not require gastric acid for absorption and is recommended for patients receiving proton pump inhibitors.^[60]

The NOF recommends at least 1000 IU units daily of vitamin D. All patients to be initiated on ADT should also be tested for vitamin D deficiency via serum 25-hydroxy vitamin D (25-OH-D).^[61] Vitamin D supplements are available as ergocalciferol (D2) or cholecalciferol (D3). There is controversy regarding the choice of agent for supplementation. In a meta-analysis of seven randomized trials evaluating serum 25-OH-D concentrations after supplementation with D2 versus D3, D3 was more efficacious at increasing serum 25-OH-D than D2, with the greatest difference seen for weekly or monthly rather than daily dosing.^[62] Those with significant vitamin D deficiency (defined as 25-OH-D below 20 ng/mL) should be aggressively repleted with vitamin D, typically 50,000 IU weekly for eight weeks.^[61]

e. Lifestyle Modifications

Lifestyle modifications are important in men receiving ADT for prostate cancer. These include smoking cessation, moderating alcohol and caffeine consumption, and regular weight bearing exercises and resistance training.^[60] Fall prevention is also critical in reducing fracture risk.^[60] Counseling patients on these modifications is essential in the care of men with prostate cancer treated with ADT and recommended interventions should be individualized.

f. Summary

Treatment-related osteoporosis can lead to increased morbidity in men treated with ADT for prostate cancer. Initial approaches for men receiving treatment with ADT include education regarding lifestyle modifications to decrease fracture risk and supplementation with calcium and vitamin D. The NOF screening and treatment guidelines (Table 3), which utilize the FRAX algorithm and BMD assessments, can be utilized to inform screening and use of

pharmacologic agents in patients with high fracture risk. For men who warrant treatment, consensus is lacking regarding the appropriate treatment agent, dose, schedule, and duration of therapy. Currently, denosumab is the only commercially available agent shown to increase bone mass and prevent fracture in high-risk men receiving ADT for prostate cancer. Other pharmacologic agents to consider include bisphosphonates, such as zoledronic acid and alendronate. Repeat BMD assessment is recommended every two years, though more frequent testing may be warranted in selected individuals.

7. Use of osteoclast-targeted therapies in metastatic castration-sensitive prostate cancer

Though osteoclast-targeted therapies are beneficial in patients with CRPC metastatic to bone, their utility has not been clearly defined in metastatic prostate cancer patients receiving first-line hormone therapy. Currently, there is no definitive evidence to support the utility of osteoclast-targeted therapies for men with metastatic castration-sensitive prostate cancer. Zoledronic acid is being evaluated in this setting in an ongoing clinical trial.^[63] Use of denosumab in men with bone metastases from prostate cancer responding to hormone therapy has not been explored. Given high response rate and hence control of cancer, ADT alone may be effective at SRE prevention.

The Medical Research Council (MRC) PR.05 study is the only completed, randomized, placebo-controlled trial to evaluate the efficacy of a bisphosphonate in metastatic castration-sensitive prostate cancer.^[64] In this study, 311 men who were initiating or responding to first-line ADT were randomized to clodronate (Clasteon) (2,080 mg orally daily) or placebo. The primary endpoint was symptomatic bone progression-free survival (PFS) or prostate cancer death. After a median follow-up of 59 months, the clodronate group showed improvements in symptomatic bone PFS (hazard ratio (HR) 0.79; 95% CI 0.61–1.02; $p=0.066$) and overall survival (OS) (HR 0.80; 95% CI 0.62–1.03; $p=0.082$), however the results were not statistically significant. At long term follow-up, treatment with clodronate was associated with statistically significant improved OS (8-year OS 22% versus 14%; HR 0.77; 95% CI 0.60–0.98; $p=0.032$).^[65] Treatment was not associated with improvement in pain or quality of life.

The Cancer and Leukemia Group B/Cancer Trials Support Unit (CALGB/CTSU) conducted a clinical trial investigating the use of zoledronic acid in men with metastatic castration-sensitive prostate cancer.^[63] The CALGB/STSU 90202 trial was designed to randomize 680 men with metastatic prostate cancer recently initiated on ADT to receive zoledronic acid (4 mg IV every 4 weeks) or placebo. The primary endpoint was time to first SRE or prostate cancer death. Cross over to the treatment arm was required for men who developed CRPC or a SRE. As of 2012, the trial stopped enrollment and follow-up is ongoing.

8. Use of osteoclast-targeted therapies in metastatic castration-resistant prostate cancer

Patients with CRPC with bone metastases are at risk for significant skeletal morbidity. Though both clodronate and pamidronate have been evaluated in this setting, zoledronic acid

is the only bisphosphonate which has shown benefit in preventing SREs in this high-risk population of men (Table 5).^[66, 67] Additionally, denosumab has shown benefit in preventing SREs in men with CRPC with bone metastases.

a. Zoledronic acid

The Zometa 039 trial evaluated the efficacy of zoledronic acid in preventing SREs in patients with CRPC with bone metastases.^[28] The study randomized 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases to zoledronic acid 4 mg IV, zoledronic acid 8 mg IV, or placebo every 3 weeks for 15 months. All men continued ADT and received any other therapy at the discretion of the treating physicians. The portion of men who experienced at least one SRE during the first 15 months of therapy was the primary endpoint of the trial. SREs were defined as pathologic bone fracture, spinal cord compression, surgery to bone, radiation to bone, or change in antineoplastic therapy to treat bone pain. The trial excluded patients with a serum creatinine > 3 mg/dL or significant hypo- or hypercalcemia. All patients received calcium and vitamin D supplementation.

Given the observation of multiple cases of nephrotoxicity early in the trial, the infusion period was increased from 5 minutes to 15 minutes and the zoledronic acid dose in the 8 mg treatment group was reduced to 4 mg. After these modifications, the rate of renal toxicity between the zoledronic acid 4 mg group and placebo were similar. The statistical plan was amended to only compare the zoledronic acid 4 mg arm to placebo at the primary study analysis. Additionally, a total of 8 patients in the zoledronic acid arms (4 in each) experienced grade 3–4 hypocalcemia.

At 15 month follow-up, the frequency of SREs was significantly reduced (33% versus 44%; $p=0.021$) and the median time to develop a SRE was significantly longer (363 versus 321 days; $p=0.002$) for those treated with zoledronic acid compared to placebo. Pain and analgesic scores were significantly higher in men who received placebo compared to zoledronic acid. The median OS was numerically longer in the zoledronic acid 4 mg group compared to the placebo group, though this was not statistically significant (546 versus 464 days; $p=0.091$). The benefit in the incidence of SREs, time to SRE development, and pain was also observed at 24 month follow-up. Based on the results of this trial, zoledronic acid became the first osteoclast-targeted agent to be approved for men with bony metastatic CRPC.

b. Denosumab

The Denosumab 103 trial was a multicenter, double-blinded, randomized, placebo-controlled study of men with CRPC and bone metastases.^[68] The study randomized 1,904 men to either treatment with denosumab (120 mg subcutaneous every 4 weeks) or zoledronic acid (4 mg IV every 4 weeks). The primary endpoint was time to first on-study SRE, which was assessed for non-inferiority. The same outcome was further assessed for superiority as a secondary endpoint. The trial excluded patients with a serum creatinine clearance < 30 mL/minute or significant hypo- or hypercalcemia. It was strongly recommended that all patients take calcium and vitamin D supplementation.

At median on-study duration of 12.2 months for the denosumab arm and 11.2 months for the zoledronic acid arm, denosumab significantly prolonged the median time to first on-study SRE compared to zoledronic acid (20.7 versus 17.1 months; $p=0.0002$ for non-inferiority; $p=0.008$ for superiority). OS and time to disease progression were similar between the treatment arms. In regards to adverse events, hypocalcemia occurred more frequently in the denosumab arm compared to the zoledronic acid arm (13% versus 5%; $p<0.0001$). Though not statistically significant, there was a trend towards a higher rate of ONJ in the denosumab arm (2% versus 1%; $p=0.09$).

c. Summary

Zoledronic acid and denosumab are beneficial in preventing SREs in men with CRPC with bone metastases. Denosumab demonstrated a slightly greater benefit in prevention of SREs compared to zoledronic acid. Additionally, the trials of zoledronic acid and denosumab for the prevention of SREs in men with metastatic CRPC were conducted in an era when patients with advanced prostate cancer had fewer treatment options for disease control. Since many new therapies for advanced prostate cancer have a beneficial impact on the rate of SREs, the choice of osteoclast-targeted agent, dose, schedule, duration of therapy, and role when used concurrently with anti-cancer agents in the modern treatment era remains an open question.

9. Prevention of bone metastases

Development of bone metastases is a clinical dilemma in patients with prostate cancer. Thus, investigation of strategies to prevent progression is logical. The efficacy of clodronate was evaluated in a phase III trial which failed to show improvement of bone-metastasis-free survival (BMFS) in patients with prostate cancer receiving ADT.^[65, 69] Though the Zometa 704 trial closed early because the event rate was lower than projected, based on the results of the European ZEUS trial recently presented at the European Association of Urology (EAU) Annual Congress, zoledronic acid had no impact in preventing bone metastases in high-risk patients receiving ADT.^[70] Though no bisphosphonate has shown benefit in bone metastases prevention, denosumab is the only drug shown to delay the onset of bone metastases in patients with CRPC.^[71]

a. Zoledronic acid

The potential for zoledronic acid prevention of bone metastases in non-metastatic high-risk prostate cancer was investigated in the European ZEUS trial.^[70] All patients in the trial had at least one high-risk feature, including PSA ≥ 20 ng/mL, lymph node positive disease, or Gleason score 8–10. In this study, 1,433 men were randomized to standard treatment with or without zoledronic acid 4 mg IV every 3 months for 48 months. All patients received calcium and vitamin D supplementation. The primary endpoint was the proportion of patients who develop on-study bone metastases. At a median follow-up of 4.9 years in the zoledronic acid group and 4.8 years in the control group, the rates of development of bone metastases were 13.7% and 13.0%, respectively ($p=0.721$). In addition, there was no difference in OS between the groups ($p=0.717$). ONJ occurred in nine patients in the zoledronic acid group and one patient in the control group.

b. Denosumab

Experimental and clinical evidence provide strong rationale for denosumab inhibition of RANKL as a promising therapeutic agent for prevention of prostate cancer progression in bone.^[72] The Denosumab 147 trial is a phase III, double-blinded, randomized, placebo-controlled study of men with non-metastatic CRPC at high-risk of bone metastases, defined as PSA ≥ 8 ug/L or PSA doubling time of ≤ 10 months, or both.^[71] The study randomized 1,432 patients to treatment with denosumab 120 mg subcutaneously or placebo every 4 weeks. The primary endpoint was BMFS. Patients were discontinued from treatment when bone metastasis occurred and received standard treatment at the discretion of the treating investigator.

Denosumab significantly increased BMFS by a median of 4.2 months compared to placebo (29.5 versus 25.2 months; $p=0.028$). In addition, denosumab significantly delayed the time to first bone metastases (32.2 versus 29.2 months; $p=0.032$). OS did not differ between groups (43.9 versus 44.8 months; $p=0.91$). In a subgroup analysis of men with a PSA doubling time of less than 6 months, denosumab prolonged BMFS by a median of 7.2 months with a 23% reduction in risk compared to placebo (25.9 versus 18.7 months; HR 0.77; 95% CI 0.64–0.93; $p=0.0064$).^[73] Treatment with denosumab was associated with increased ONJ (5% versus 0%) and hypocalcemia (2% versus $<1\%$) compared to placebo. This study failed to show an effect on quality of life, pain, and OS.

Given that the degree of benefit was similar between the pre-metastatic and metastatic setting, there is concern that the study included patients with established metastases that were undetectable by existing imaging studies. The appropriate sequence of denosumab in the current treatment landscape for prostate cancer requires further investigation.

c. Summary

Prevention of bone metastases in patients with non-metastatic CRPC remains an area for further investigation. Recently zoledronic acid was shown to have no impact in preventing bone metastases in patients with high-risk prostate cancer. Denosumab is the only agent shown to delay the time to bone metastases, however the magnitude of clinical benefit is less certain.

10. Radiopharmaceuticals

Radiopharmaceuticals have emerged as a treatment strategy for patients with CRPC and symptomatic bone metastases. These compounds are systemically administered agents that localize to sites of bone metastases and deliver focal radiation through β -emission (strontium-89 (Metastron), samarium-153 (Quadramet)) or α -emission (radium-223) (Table 6). Under ideal circumstances, the physical half-life of the isotopes should be long enough to enable sufficient therapeutic effect, but short enough to limit myelotoxicity.^[74] Additionally, the range of emission should be narrow to limit marrow toxicity. Strontium-89 and samarium-153 are currently used for the palliation of pain in patients with CRPC with symptomatic bone metastases. Radium-223 is the first radiopharmaceutical agent to demonstrate improved survival in patients with CRPC with symptomatic bone metastases.

Strontium-89 and samarium-153 are useful for the palliation of pain due to bone metastases. They are contraindicated in patients with pathologic fractures, spinal cord compression, significant myelosuppression or renal dysfunction.^[74] Despite the beneficial palliative effect observed with strontium-89 and samarium-153, these agents have had relatively limited clinical use, likely related to logistics of administration, myelotoxicity, availability of alternative treatment strategies, and other factors. Recently, the positive impact of radium-223 on OS is a landmark development that may expand the utility of radiopharmaceuticals in the treatment of patients with symptomatic bone metastatic CRPC.

a. Strontium-89

The first use of a radiopharmaceutical was with strontium-89 in 1942. Strontium-89 is a calcium analogue with a long half-life (50.5 days) and relatively high-energy average β -emission (0.58 MeV).^[74] The average soft tissue range of this agent is 2.4 mm.^[74] It has been in use for the palliation of pain associated with symptomatic bone metastases in patients with CRPC since 1993 based on the results of several randomized clinical trials.^[75, 76]

A British trial of 284 men randomly assigned to treatment with strontium-89 or external beam radiation (focal or hemibody) showed similar rates of pain control between the treatment arms, however fewer patients reported new pain sites after strontium-89 treatment.^[76] A phase III, placebo-controlled trial randomized 126 men treated with focal external beam radiation to treatment with strontium-89 or placebo.^[75] Though there was no difference in OS between the two groups, patients given strontium-89 had decreased analgesic use, increased time to further radiation therapy, and decreased number of new painful sites.

b. Samarium-153

Samarium-153 binds to hydroxyapatite crystals in areas of high bone turnover and has low-energy average β -emission (0.22 MeV) with a relatively short half-life (1.9 days).^[74] The average soft tissue range of this agent is 0.6 mm.^[74] The kidneys are the main route of elimination of unbound samarium-153 with complete excretion in 6 hours.^[74]

Clinical benefit as evidenced by pain control was demonstrated in clinical trials.^[77, 78] In a phase III, double-blinded, randomized, placebo-controlled trial, 118 patients with symptomatic bone metastases, of which 68% had prostate cancer, were randomized to 1 of 2 doses of samarium-153 (0.5 mCi/kg or 1.0 mCi/kg) or placebo.^[78] Compared to placebo, the higher dose of samarium-153 was associated with significantly less pain and decreased analgesic use. There was no difference in OS between the groups. Toxicity profiles were comparable with transient thrombocytopenia and leukopenia with samarium-153 treatment. Another phase III, double-blinded, placebo-controlled trial randomized 152 men with bone metastatic CRPC to samarium-153 or a nonradioactive samarium placebo.^[77] Patients receiving samarium-153 had significant improvement of pain and decreased analgesic use, though there was no difference in OS between the treatment arms. Transient myelosuppression was the only significant adverse side effect.

c. Radium-223

Radium-223 is an alpha emitting radioisotope which acts as a calcium-mimic with natural bone-seeking proclivity.^[74] In contrast to β -particles, α -particles provide more dense ionizing radiation in a narrow range of <0.1 mm, corresponding to 2–10 cell diameters, thus minimizing myelotoxicity.^[79] The particles induce DNA double-strand breaks leading to cell death at all stages of the cell cycle.^[79] Radium-223 has a suitable half-life (11.4 days) and particles not taken up by bone are rapidly cleared to the gut and excreted.^[74]

The efficacy of radium-223 was demonstrated in the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial.^[80, 81] This phase III, international, double-blinded, trial randomized 922 men with CRPC with bone metastases to radium-223 plus best supportive care or placebo plus best supportive care. Eligible patients had ≥ 2 symptomatic bone metastases, no known visceral metastases, and had either received prior docetaxel (Taxotere) or were unfit for docetaxel chemotherapy. Patients were randomized 2:1 to receive six injections of radium-223 (50 kBq/kg) at 4-week intervals. The primary endpoint was OS. Patients were stratified by prior docetaxel use, baseline alkaline phosphatase, and current bisphosphonate use. Updated results were presented at the 2012 American Society of Clinical Oncology (ASCO) meeting. Based on data from a planned interim analysis of 809 patients, radium-223 significantly improved median OS (14 versus 11.2 months; $p=0.00185$). In addition, SREs were lower and time to first SRE was significantly delayed in the treatment arm compared to placebo (13.6 versus 8.4 months; $p=0.00046$). There was a low incidence of grade 3–4 myelosuppression (1.8% neutropenia and 0.8% thrombocytopenia).

11. Non-bone targeted therapies documented to decrease skeletal-related events

The development of novel therapeutics is transforming the treatment paradigm of advanced prostate cancer. Agents that are active in controlling the burden of disease and improving survival likely diminish the negative effects of bone metastases. SREs, which have classically been an endpoint of trials assessing efficacy of osteoclast-targeted agents, are being evaluated in trials of novel systemic agents. Abiraterone and enzalutamide have recently been shown to improve OS and have a beneficial impact on decreasing the rate of SREs in patients with metastatic CRPC. In addition to novel hormone therapies, other potential targets important in the development of bone metastases include MET, a receptor tyrosine kinase, and Src, a non-receptor tyrosine kinase.^[82, 83]

a. Abiraterone

Abiraterone irreversibly inhibits the CYP17 enzyme, thus blocking androgen synthesis in the testis, adrenal glands, and prostatic tumor cells.^[84] The activity of abiraterone was demonstrated in a phase III trial in which 1,195 men previously treated with docetaxel were randomly assigned to abiraterone plus prednisone or placebo plus prednisone.^[84] After a median follow-up of 13 months, abiraterone significantly increased OS compared to placebo (median 14.8 versus 10.9 months; $p<0.0001$). Notably, abiraterone delayed the median time

to SRE (25 versus 20.3 months; $p=0.0001$) and significantly decreased pain compared to placebo.^[85]

b. Enzalutamide

Enzalutamide is a novel androgen receptor (AR) signaling inhibitor which competitively inhibits binding of androgens to the AR, inhibits AR nuclear translocation, and inhibits association of the AR with DNA.^[86] In a global, phase III, double-blinded, placebo-controlled trial, 1,199 men with advanced prostate cancer previously treated with docetaxel were randomized to enzalutamide versus placebo in a 2:1 ratio.^[87] The primary endpoint was OS. The study was stopped after a planned interim analysis at the time of 520 deaths. Treatment with enzalutamide was associated with improved OS (18.4 versus 13.6 months; $p<0.0001$). In addition, time to first SRE was significantly longer in the treatment arm compared to placebo (8.3 versus 2.9 months; $p=0.001$).

12. Conclusions

Bone health is a critical issue in patients with prostate cancer. Strategies to reduce morbidity associated with treatment-related osteoporosis include lifestyle modifications, calcium and vitamin D supplementation, and pharmacologic intervention with osteoclast-targeted agents in patients with or at high-risk of osteoporotic fractures. The mainstay of care for the management of bone metastases includes effective therapies to control the burden of disease, and in patients with CRPC, osteoclast-targeted agents. As improved therapeutics populate the treatment landscape, additional studies will need to investigate the optimal dosing, schedule, duration, and role of osteoclast-targeted agents with concurrent administration of anti-cancer agents in the treatment of patients with metastatic disease.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012; 62(1):10–29. [PubMed: 22237781]
2. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature*. 2003; 423(6937):337–342. [PubMed: 12748652]
3. Lacey DL, Boyle WJ, Simonet WS, et al. Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. *Nat Rev Drug Discov*. 2012; 11(5):401–419. [PubMed: 22543469]
4. Schoppet M, Preissner KT, Hofbauer LC. RANK ligand and osteoprotegerin: paracrine regulators of bone metabolism and vascular function. *Arterioscler Thromb Vasc Biol*. 2002; 22(4):549–553. [PubMed: 11950689]
5. Gaur T, Lengner CJ, Hovhannisyan H, et al. Canonical WNT signaling promotes osteogenesis by directly stimulating Runx2 gene expression. *J Biol Chem*. 2005; 280(39):33132–33140. [PubMed: 16043491]
6. Bilezikian JP. Osteoporosis in men. *J Clin Endocrinol Metab*. 1999; 84(10):3431–3434. [PubMed: 10522975]

7. Gilbert SM, Kuo YF, Shahinian VB. Prevalent and incident use of androgen deprivation therapy among men with prostate cancer in the United States. *Urol Oncol*. 2011; 29(6):647–653. [PubMed: 19926311]
8. Barry MJ, Delorenzo MA, Walker-Corkery ES, et al. The rising prevalence of androgen deprivation among older American men since the advent of prostate-specific antigen testing: a population-based cohort study. *BJU Int*. 2006; 98(5):973–978. [PubMed: 16879443]
9. Daniell HW, Dunn SR, Ferguson DW, et al. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. *J Urol*. 2000; 163(1):181–186. [PubMed: 10604342]
10. Greenspan SL, Coates P, Sereika SM, et al. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J Clin Endocrinol Metab*. 2005; 90(12):6410–6417. [PubMed: 16189261]
11. Mittan D, Lee S, Miller E, et al. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. *J Clin Endocrinol Metab*. 2002; 87(8):3656–3661. [PubMed: 12161491]
12. Diamond TH, Higano CS, Smith MR, et al. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. *Cancer*. 2004; 100(5):892–899. [PubMed: 14983482]
13. Guise TA, Oefelein MG, Eastham JA, et al. Estrogenic side effects of androgen deprivation therapy. *Rev Urol*. 2007; 9(4):163–180. [PubMed: 18231613]
14. Lee H, McGovern K, Finkelstein JS, et al. Changes in bone mineral density and body composition during initial and long-term gonadotropin-releasing hormone agonist treatment for prostate carcinoma. *Cancer*. 2005; 104(8):1633–1637. [PubMed: 16116596]
15. Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med*. 2005; 352(2):154–164. [PubMed: 15647578]
16. Smith MR, Lee WC, Brandman J, et al. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. *J Clin Oncol*. 2005; 23(31):7897–7903. [PubMed: 16258089]
17. Oefelein MG, Ricchiuti V, Conrad W, et al. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. *J Urol*. 2002; 168(3):1005–1007. [PubMed: 12187209]
18. Khosla S, Oursler MJ, Monroe DG. Estrogen and the skeleton. *Trends Endocrinol Metab*. 2012; 23(11):576–581. [PubMed: 22595550]
19. Falahati-Nini A, Riggs BL, Atkinson EJ, et al. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. *J Clin Invest*. 2000; 106(12):1553–1560. [PubMed: 11120762]
20. Mellstrom D, Vandenput L, Mallmin H, et al. Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. *J Bone Miner Res*. 2008; 23(10):1552–1560. [PubMed: 18518773]
21. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med*. 2001; 345(13):948–955. [PubMed: 11575286]
22. Amin S, Zhang Y, Felson DT, et al. Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study. *Am J Med*. 2006; 119(5):426–433. [PubMed: 16651055]
23. Khosla S, Melton LJ 3rd, Atkinson EJ, et al. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *J Clin Endocrinol Metab*. 1998; 83(7):2266–2274. [PubMed: 9661593]
24. Rochira V, Balestrieri A, Madeo B, et al. Osteoporosis and male age-related hypogonadism: role of sex steroids on bone (patho)physiology. *Eur J Endocrinol*. 2006; 154(2):175–185. [PubMed: 16452530]
25. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004; 351(15):1502–1512. [PubMed: 15470213]
26. Keller ET, Brown J. Prostate cancer bone metastases promote both osteolytic and osteoblastic activity. *J Cell Biochem*. 2004; 91(4):718–729. [PubMed: 14991763]

27. Norgaard M, Jensen AO, Jacobsen JB, et al. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). *J Urol*. 2010; 184(1):162–167. [PubMed: 20483155]
28. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002; 94(19):1458–1468. [PubMed: 12359855]
29. Cook RJ, Coleman R, Brown J, et al. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clin Cancer Res*. 2006; 12(11 Pt 1):3361–3367. [PubMed: 16740758]
30. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med*. 2004; 350(16):1655–1664. [PubMed: 15084698]
31. Rogers MJ, Watts DJ, Russell RG. Overview of bisphosphonates. *Cancer*. 1997; 80(8 Suppl):1652–1660. [PubMed: 9362432]
32. Fleisch H. Bisphosphonates: mechanisms of action. *Endocr Rev*. 1998; 19(1):80–100. [PubMed: 9494781]
33. Papapoulos SE. Bisphosphonates: how do they work? *Best Pract Res Clin Endocrinol Metab*. 2008; 22(5):831–847. [PubMed: 19028359]
34. van Beek ER, Cohen LH, Leroy IM, et al. Differentiating the mechanisms of antiresorptive action of nitrogen containing bisphosphonates. *Bone*. 2003; 33(5):805–811. [PubMed: 14623056]
35. Plotkin LI, Lezcano V, Thostenson J, et al. Connexin 43 is required for the anti-apoptotic effect of bisphosphonates on osteocytes and osteoblasts in vivo. *J Bone Miner Res*. 2008; 23(11):1712–1721. [PubMed: 18597631]
36. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. *Kidney Int*. 2008; 74(11):1385–1393. [PubMed: 18685574]
37. Khan AA, Sandor GK, Dore E, et al. Bisphosphonate associated osteonecrosis of the jaw. *J Rheumatol*. 2009; 36(3):478–490. [PubMed: 19286860]
38. Southwest Oncology Group. [Accessed 2012 Dec 5] Osteonecrosis of the jaw in patients with cancer receiving zoledronic acid for bone metastases [ClinicalTrials.gov identifier NCT00874211]. US National Institutes of Health, [ClinicalTrials.gov](http://www.clinicaltrials.gov). [online]. Available from URL: <http://www.clinicaltrials.gov>
39. Dalle Carbonare L, Zanatta M, Gasparetto A, et al. Safety and tolerability of zoledronic acid and other bisphosphonates in osteoporosis management. *Drug Healthc Patient Saf*. 2010; 2:121–137. [PubMed: 21701624]
40. Lee RJ, Saylor PJ, Smith MR. Contemporary therapeutic approaches targeting bone complications in prostate cancer. *Clin Genitourin Cancer*. 2010; 8(1):29–36. [PubMed: 21208853]
41. Block GA, Bone HG, Fang L, et al. A single-dose study of denosumab in patients with various degrees of renal impairment. *J Bone Miner Res*. 2012; 27(7):1471–1479. [PubMed: 22461041]
42. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009; 361(8):756–765. [PubMed: 19671655]
43. Cummings SR, Cawthon PM, Ensrud KE, et al. BMD and risk of hip and nonvertebral fractures in older men: a prospective study and comparison with older women. *J Bone Miner Res*. 2006; 21(10):1550–1556. [PubMed: 16995809]
44. Kanis JA, Melton LJ 3rd, Christiansen C, et al. The diagnosis of osteoporosis. *J Bone Miner Res*. 1994; 9(8):1137–1141. [PubMed: 7976495]
45. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ*. 1996; 312(7041):1254–1259. [PubMed: 8634613]
46. Schuit SC, van der Klift M, Weel AE, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone*. 2004; 34(1):195–202. [PubMed: 14751578]
47. Donaldson MG, Cawthon PM, Lui LY, et al. Estimates of the proportion of older white men who would be recommended for pharmacologic treatment by the new US National Osteoporosis Foundation guidelines. *J Bone Miner Res*. 2010; 25(7):1506–1511. [PubMed: 20200971]

48. Saylor PJ, Kaufman DS, Michaelson MD, et al. Application of a fracture risk algorithm to men treated with androgen deprivation therapy for prostate cancer. *J Urol*. 2010; 183(6):2200–2205. [PubMed: 20399451]
49. Diamond TH, Winters J, Smith A, et al. The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: a double blind, randomized, placebo-controlled crossover study. *Cancer*. 2001; 92(6):1444–1450. [PubMed: 11745221]
50. Klotz LH, McNeill IY, Kebedjian M, et al. A Phase 3, Double-blind, Randomised, Parallel-group, Placebo-controlled Study of Oral Weekly Alendronate for the Prevention of Androgen Deprivation Bone Loss in Nonmetastatic Prostate Cancer: The Cancer and Osteoporosis Research with Alendronate and Leuprolide (CORAL) Study. *Eur Urol*. 2013; 63(5):927–935. [PubMed: 23040208]
51. Michaelson MD, Kaufman DS, Lee H, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J Clin Oncol*. 2007; 25(9):1038–1042. [PubMed: 17369566]
52. Morabito N, Gaudio A, Lasco A, et al. Neridronate prevents bone loss in patients receiving androgen deprivation therapy for prostate cancer. *J Bone Miner Res*. 2004; 19(11):1766–1770. [PubMed: 15476575]
53. Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol*. 2003; 169(6):2008–2012. [PubMed: 12771706]
54. Serpa Neto A, Tobias-Machado M, Esteves MA, et al. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*. 2012; 15(1):36–44. [PubMed: 21894175]
55. Saylor PJ, Lee RJ, Smith MR. Emerging therapies to prevent skeletal morbidity in men with prostate cancer. *J Clin Oncol*. 2011; 29(27):3705–3714. [PubMed: 21860001]
56. Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med*. 2009; 361(8):745–755. [PubMed: 19671656]
57. Smith MR, Fallon MA, Lee H, et al. Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab*. 2004; 89(8):3841–3846. [PubMed: 15292315]
58. Smith MR, Morton RA, Barnette KG, et al. Toremifene to reduce fracture risk in men receiving androgen deprivation therapy for prostate cancer. *J Urol*. 2010; 184(4):1316–1321. [PubMed: 20723926]
59. Chung M, Lee J, Terasawa T, et al. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011; 155(12):827–838. [PubMed: 22184690]
60. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health in Cancer Care. *J Natl Compr Canc Netw*. 2009; 7(3):S1–S32. quiz S3-5. [PubMed: 19555589]
61. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007; 357(3):266–281. [PubMed: 17634462]
62. Tripkovic L, Lambert H, Hart K, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr*. 2012; 95(6):1357–1364. [PubMed: 22552031]
63. Cancer and Leukemia Group B. [Accessed 2012 Nov 21] Zoledronate in preventing skeletal (bone)-related events in patients who are receiving androgen deprivation therapy for prostate cancer and bone metastases [ClinicalTrials.gov identifier NCT00079001]. US National Institutes of Health, [ClinicalTrials.gov](http://www.clinicaltrials.gov). [online]. Available from URL: <http://www.clinicaltrials.gov>
64. Dearnaley DP, Sydes MR, Mason MD, et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J Natl Cancer Inst*. 2003; 95(17):1300–1311. [PubMed: 12953084]
65. Dearnaley DP, Mason MD, Parmar MK, et al. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC

- PR04 and PR05 randomised controlled trials. *Lancet Oncol.* 2009; 10(9):872–876. [PubMed: 19674936]
66. Ernst DS, Tannock IF, Winkler EW, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol.* 2003; 21(17):3335–3342. [PubMed: 12947070]
 67. Small EJ, Smith MR, Seaman JJ, et al. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol.* 2003; 21(23):4277–4284. [PubMed: 14581438]
 68. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet.* 2011; 377(9768):813–822. [PubMed: 21353695]
 69. Mason MD, Sydes MR, Glaholm J, et al. Oral sodium clodronate for nonmetastatic prostate cancer--results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). *J Natl Cancer Inst.* 2007; 99(10):765–776. [PubMed: 17505072]
 70. Witjes W, Tammela T, Wirth M. Effectiveness of zoledronic acid for the prevention of bone metastases in high risk prostate cancer patients: A randomised, open label, multicenter study of the European Association of Urology (EAU) in cooperation with the Scandinavian Prostate Cancer Group (SPCG) and the Arbeitsgemeinschaft Urologische Onkologie (AUO). An initial report of the "ZEUS" study. *ASCO Meeting Abstracts.* 2006; 24(18_suppl):14644.
 71. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet.* 2012; 379(9810):39–46. [PubMed: 22093187]
 72. Guise TA, Mohammad KS, Clines G, et al. Basic mechanisms responsible for osteolytic and osteoblastic bone metastases. *Clin Cancer Res.* 2006; 12(20 Pt 2):6213s–6216s. [PubMed: 17062703]
 73. Saad F, Smith MR, Shore ND, et al. Effect of denosumab on prolonging bone-metastasis free survival (BMFS) in men with nonmetastatic castrate-resistant prostate cancer (CRPC) presenting with aggressive PSA kinetics. *ASCO Meeting Abstracts.* 2012; 30(15_suppl):4510.
 74. Goyal J, Antonarakis ES. Bone-targeting radiopharmaceuticals for the treatment of prostate cancer with bone metastases. *Cancer Lett.* 2012; 323(2):135–146. [PubMed: 22521546]
 75. Porter AT, McEwan AJ, Powe JE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys.* 1993; 25(5):805–813. [PubMed: 8478230]
 76. Quilty PM, Kirk D, Bolger JJ, et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol.* 1994; 31(1):33–40. [PubMed: 7518932]
 77. Sartor O, Reid RH, Hoskin PJ, et al. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology.* 2004; 63(5):940–945. [PubMed: 15134985]
 78. Serafini AN, Houston SJ, Resche I, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol.* 1998; 16(4):1574–1581. [PubMed: 9552068]
 79. Nilsson S, Larsen RH, Fossa SD, et al. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. *Clin Cancer Res.* 2005; 11(12):4451–4459. [PubMed: 15958630]
 80. Parker C, Nilsson S, Heinrich D, et al. Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA). *J Clin Oncol.* 2012; 30(suppl) abstr LBA4512.
 81. Sartor AO, Heinrich D, O'Sullivan JM, et al. Radium-223 chloride (Ra-223) impact on skeletal-related events (SREs) and ECOG performance status (PS) in patients with castration-resistant prostate cancer (CRPC) with bone metastases: Interim results of a phase III trial (ALSYMPCA). *J Clin Oncol.* 2012; 30(suppl) abstr 4551.

82. Peters S, Adjei AA. MET: a promising anticancer therapeutic target. *Nat Rev Clin Oncol*. 2012; 9(6):314–326. [PubMed: 22566105]
83. Saad F, Lipton A. SRC kinase inhibition: targeting bone metastases and tumor growth in prostate and breast cancer. *Cancer Treat Rev*. 2010; 36(2):177–184. [PubMed: 20015594]
84. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011; 364(21):1995–2005. [PubMed: 21612468]
85. Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol*. 2012
86. Arakawa H, Nakanishi T, Yanagihara C, et al. Enhanced expression of organic anion transporting polypeptides (OATPs) in androgen receptor-positive prostate cancer cells: possible role of OATP1A2 in adaptive cell growth under androgen-depleted conditions. *Biochem Pharmacol*. 2012; 84(8):1070–1077. [PubMed: 22864060]
87. Lester JE, Dodwell D, Horsman JM, et al. Current management of treatment-induced bone loss in women with breast cancer treated in the United Kingdom. *Br J Cancer*. 2006; 94(1):30–35. [PubMed: 16317429]
88. National Osteoporosis Foundation. Clinicians's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2010.

Key Points

- Patients with prostate cancer are at increased risk of skeletal complications.
- Treatment-related osteoporosis is an established risk for patients receiving androgen deprivation therapy.
- Several agents including bisphosphonates, receptor activator of nuclear factor- κ B ligand inhibitors, and selective estrogen receptor modulators have shown benefit in the management of treatment-related osteoporosis.
- Patients with bone metastases from prostate cancer are at increased risk of skeletal-related events.
- Zoledronic acid and denosumab are effective in preventing skeletal-related events in patients with castration-resistant prostate cancer with bone metastases.
- Radium-223, a radiopharmaceutical targeting bone, is effective at preventing skeletal-related events and improving survival in patients with metastatic castration-resistant prostate cancer.
- Systemic agents, including abiraterone and enzalutamide, are active in preventing SREs, given efficacy in disease control.

Figure 1. Normal bone physiology

The skeleton is a metabolically active organ that undergoes continuous remodeling, a dynamic process of bone resorption by osteoclasts and bone formation by osteoblasts. Osteoblasts and bone marrow stromal cells release RANKL, which binds to RANK on mononuclear osteoclast precursor cells. This process promotes osteoclast differentiation and activation. Mature, multi-nucleated osteoclasts bind to the bone matrix, form a resorption lacunae, into which they secrete acid and lytic enzymes, leading to bone resorption. Osteoblasts, which arise from osteoprogenitor cells, form a cell layer over the bone surface, on which the matrix is formed and subsequently mineralized to become bone.^[2]

Figure 2. The vicious cycles of bone metastases

Interactions between tumor cells and the bone microenvironment cause bone destruction via osteoclast activation and tumor growth. Tumor cells secrete cytokines and factors which activate osteoblasts to produce RANKL and downregulate OPG. This leads to activation of osteoclast precursors and subsequent osteolysis. The process of bone resorption releases TGF- β , PDGF, FGF, BMPs which promote tumor cell proliferation and further production of pro-resorptive factors, including PTHrH, macrophage colony stimulating factor (M-CSF), TNF, IL-6. This leads to a vicious cycles of osteolysis and tumor growth.^[30]

Figure 3. Basic structure of a bisphosphonate

Bisphosphonate are synthetic analogues to naturally occurring inorganic pyrophosphate. The two phosphate groups (PO_3) bound to a carbon determine the name bisphosphonate. The R_1 side chain mainly influences pharmacokinetics of the drug, while the R_2 side chain determines mechanism of action and potency.^[31]

Table 1Potency of Bisphosphonates.^[32]

Agent	Relative Potency
Non-nitrogen containing bisphosphonates	
First-generation	
Etidronate	1
Clodronate	10
Nitrogen containing bisphosphonates	
Second-generation	
Alendronate	100
Pamidronate	100–1,000
Third-generation	
Neridronate	100
Risedronate	1000–10,000
Ibandronate	1000–10,000
Zoledronate	>10,000

Table 2

Pharmacokinetics of zoledronic acid and denosumab.^[32, 41]

Drug	Mechanism of Action	Bioavailability	T _{1/2} (days)	Clearance	Dose Modification
Zoledronic acid	Binds to hydroxyapatite crystals on exposed bone	1% (oral), 100% (intravenous)	Triphasic	Renal	Yes*
Denosumab	Monoclonal antibody to RANKL	62% (subcutaneous)	25	RES	No**

RES: Reticuloendothelial system.

* Dose modification is based on renal function. Trials of zoledronic acid in men with prostate cancer excluded patients with creatinine clearance < 30 mL/minute. Use is not recommended in patients with creatinine clearance < 30 mL/minute or on dialysis given risk of hypocalcemia and worsening renal function.

** No adjustment is necessary when administered every 6 months. Once-monthly dosing has not been evaluated in patients with renal impairment. Patients with creatinine clearance < 30 mL/minute or on dialysis require close monitoring due to increased risk of hypocalcemia.

Table 3NOF Screening and Treatment Recommendations.^[88]

Screening Recommendations:	All men age 70 years or older
	Adults who have a fracture after age 50
	Adults with a condition or taking a medicine associated with low bone mass or bone loss
	Anyone being considered for pharmacologic therapy for osteoporosis
	Anyone being treated for osteoporosis, to monitor treatment effect
Men ≥ 50 years of age presenting with the following should be considered for treatment:	Hip or vertebral fracture (both clinical or radiological)
	T-score ≤ -2.5 at the femoral neck or spine after evaluation to exclude secondary causes
	Low bone mass as defined by T-score between -1.0 and -2.5 at the femoral neck or spine and 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO/FRAX algorithm (www.shef.ac.uk/FRAX/)

Table 4
Trials of osteoclast-targeted therapies for prevention of treatment-related fragility fractures.

Trial	Number of Patients	Population	Treatment	Primary Endpoint	Outcome
Denosumab Halt 138 ^[56]	1,468	Men with nonmetastatic prostate cancer treated with ADT at high risk of fracture (age ≥ 70 years, low BMD, or history of osteoporotic fracture)	Denosumab 60 mg subcutaneous every 6 months vs. placebo × 2 years	Percent change in BMD at lumbar spine at 24 months	Improvement in BMD at all sites and decreased incidence of new vertebral fractures (1.5% versus 3.9%; p=0.006)
Toremifene ^[58]	1,284	Men with nonmetastatic prostate cancer treated with ADT at high risk of fracture (age ≥ 70 years or low BMD)	Toremifene 80 mg orally daily vs. placebo × 2 years	Incidence of new vertebral fractures	Improvement in BMD at all sites and decreased incidence of new vertebral fractures (2.5% versus 4.9%; p=0.05)

Table 5

Trials of osteoclast-targeted therapies in CRPC.

Trial	Number of Patients	Population	Treatment	Primary Endpoint	Outcome
Prevention of bone metastases in patients with CRPC					
Denosumab 147 ^[71]	1,432	CRPC at high-risk of developing metastases (PSA ≥ 8 ug/L or PSA doubling time of ≤ 10 months, or both)	Denosumab 120 mg subcutaneously vs. placebo every 4 weeks	BMFS	Increased BMFS (29.5 vs. 25.2; p=0.0028) and delayed time to first bone metastases (32.2 versus 29.2 months; p=0.032)
Prevention of SREs in patients with CRPC					
Zometa 039 ^[28]	643	Men with CRPC and asymptomatic or minimally symptomatic bone metastases	Zoledronic acid IV (4 mg or 8 mg) vs. placebo every 3 weeks × 15 months	Portion of men who experienced one SRE during the first 15 months of therapy	Decreased frequency of SREs (33% versus 44%; p=0.021) and increased time to develop SRE (363 versus 321 days; p=0.002)
Denosumab 103 ^[68]	1,904	Men with CRPC with bone metastases	Denosumab 120 mg subcutaneous vs. zoledronic acid 4 mg IV every 4 weeks	Time to first on-study SRE	Increased time to first on-study SRE (20.7 versus 17.1 months; p=0.0008 for superiority)

Table 6Physical characteristics of radiopharmaceuticals for prostate cancer.^[74]

Radiopharmaceutical	T _{1/2} (days)	Mean β Energy (MeV)	Mean α Energy (MeV)	Mean Tissue Penetration (mm)
Strontium-89	50.5	0.58	–	2.4
Samarium-153	1.9	0.22	–	0.6
Radium-223	11.4	–	5.64	<0.1