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Contemporary Therapeutic Approaches Targeting Bone Complications in Prostate Cancer

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Abstract

Skeletal complications are major causes of morbidity in patients with prostate cancer. Despite the osteoblastic appearance of prostate cancer bone metastases, elevated serum and urinary markers of bone resorption are indicative of high osteoclast activity. Increased osteoclast activity is independently associated with subsequent skeletal complications, disease progression, and death. Osteoclast-targeted therapies aim to reduce the risk for disease-related skeletal complications, bone metastases, and treatment-related fractures. This review focuses on recent advances in osteoclast-targeted therapies in the treatment and prevention of bone complications in prostate cancer. Osteoclast-targeted therapies have been extensively studied in men with prostate cancer. The potent bisphosphonate zoledronic acid significantly decreased the risk of skeletal complications in men with castration-resistant prostate cancer and bone metastases, and is Federal Drug Administration approved for this indication. Denosumab is a human monoclonal antibody that inhibits receptor activator of nuclear factor-κB (RANK) ligand, a critical mediator of osteoclast differentiation, activation, and survival. Data from recent phase III clinic trials demonstrate the emerging role for denosumab in the treatment of prostate cancer bone metastases and prevention of fractures associated with androgen deprivation therapy.

Keywords

Bisphosphonate; Denosumab; Osteoclast; RANKL; Toremifene; Zoledronic acid

Clinical Manifestations of Bone Complications in Prostate Cancer

In 2009, prostate cancer accounted for 25% of all cancer diagnoses in men and over 27,000 deaths from metastatic disease in the United States.[1] Bone metastases are a major burden to men with prostate cancer as they are present in 80%-90% of men with metastatic castration-resistant prostate cancer (CRPC).[2,3] Bone metastases are most common in the vertebral column, pelvis, ribs, long bones, and skull. Bone metastases from prostate cancer are predominantly osteoblastic in appearance on plain films.

The most common symptom of bone metastases from prostate cancer is pain. Metastases to vertebral bones can cause spinal cord compression, compression fractures, nerve root compression, and cauda equina syndrome. Pathologic fractures of proximal long bones can occur but are less common than vertebral fractures.[4] Excessive osteoblastic bone deposition causes hypocalcemia and secondary hyperparathyroidism.[5] Ineffective erythropoiesis can be caused by both bone metastases and cancer therapies.

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Fragility fractures are common in older men.[6] Hypogonadism, chronic glucocorticoid therapy, and excessive alcohol intake are among the most common risk factors for developing osteoporosis in men.[7] Androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) agonist causes severe hypogonadism and significantly increases fracture risk.[8,9]

Both the biology and the treatment of advanced prostate cancer therefore cause detrimental changes in bone integrity and significant clinical consequences. This review will discuss opportunities for osteoclast-targeted therapeutic intervention and clinical trial data in prostate cancer for the following settings: (1) treatment of bone metastases to prevent skeletal complications; (2) prevention of bone metastasis; and (3) prevention of bone loss and consequent risk of fracture because of androgen deprivation.

Normal Bone Physiology

The normal integrity of adult bone is maintained by a careful balance between bone resorption by osteoclasts and bone formation by osteoblasts. Osteoclasts are tissue-specific macrophages and can be activated by local and systemic factors to resorb bone. Activated osteoclasts bind to bone to create an acidified resorption vacuole, into which they release proteases that dissolve the matrix and liberate growth factors, further enriching the marrow's growth factor milieu.[10,11]

Receptor activator of nuclear factor-κB (RANK) signaling is a central regulator of osteoclast differentiation, activation, and survival. Osteoclasts express RANK, a member of the tumor necrosis factor (TNF) receptor superfamily. RANK is activated by RANK ligand (RANKL), a protein that is expressed by bone marrow stromal cells and osteoblasts. Osteoprotegerin (OPG) is a decoy receptor for RANKL expressed by osteoblasts and other tissues and negatively regulates bone resorption.[12] The ratio of RANKL to OPG therefore determines osteoclast activity. Animal studies have demonstrated the importance of the RANKL/OPG ratio: targeted deletion of OPG causes osteopenia,[13] whereas overexpression of OPG in transgenic mice causes osteopetrosis.[14]

Pathophysiology of Bone Metastasis From Prostate Cancer

The propensity of cancer to metastasize to bone is likely because of a combination of high blood flow to bone marrow, a rich growth factor milieu, and a large repository of immobilized growth factors in the matrix.[11] Prostate cancer metastasis in bone is largely osteoblastic, but the woven bone contained in bone metastases is structurally weak and associated with increased fracture risk.[15]

Despite their osteoblastic radiographic appearance, prostate cancer metastases are associated with increased osteoclastic activity.[4,15,16] Consistent with a high bone turnover state, markers of bone resorption, such as urine N-telopeptide (NTx) and bone-specific alkaline phosphatase, are elevated in patients with osteoblastic bone metastasis from prostate cancer.[17,18] Prostate cancer–mediated osteoclast activation is independently associated with risk for subsequent skeletal complications, disease progression, and death.[4,19]

Osteoblast-driven calcium-phosphate deposition causes hypocalcemia, which stimulates parathyroid hormone (PTH) production and secondary hyperparathyroidism. The PTH induces RANKL expression in bone marrow stromal cells and osteoblasts. Subsequent RANK signaling in turn stimulates osteoclast differentiation and activation. Bone matrix degradation by osteoclasts liberates growth factors, further stimulating tumor cell proliferation in bone, completing a vicious cycle of progressive metastatic disease.

It is uncertain whether bone resorption precedes osteoblastic metastatic development or is a consequence of increased bone formation. In a mouse model of prostate cancer, inhibition of osteoclast activity by zoledronic acid (ZA) did not inhibit the development of osteoblastic metastases.[20]

Therapeutic inhibition of osteoblast activity is a rational target in prostate cancer. The development of atrasentan, an endothelin antagonist, and other modulators of osteoblastic activity in prostate cancer are reviewed elsewhere.[21]

Pathophysiology of Prostate Cancer Therapy–Induced Osteoporosis

Prostate cancer treatments affect bone integrity. Androgen deprivation therapy (ADT) is the first-line treatment for metastatic prostate cancer. ADT is also routinely used in conjunction with radiation as primary therapy for men with intermediate- or high-risk early-stage prostate cancer. ADT can be accomplished by either surgical castration (bilateral orchiectomies) or medical castration (chronic therapy with a GnRH agonist or antagonist). The intended therapeutic effect of ADT is severe hypogonadism, with modern assays showing that medical castration generally lowers serum testosterone to < 20 ng/mL.[22,23]

Profound hypogonadism is associated with metabolic changes including decreased bone mineral density (BMD).[24] ADT increases PTH-mediated osteoclast activation, and is associated with increased biochemical markers of osteoblast and osteoclast activity.[25,26] ADT raises the risk of fracture in patients with prostate cancer.[8,9] In analyses of over 50,000 patients in the Surveillance, Epidemiology and End Results (SEER) program and Medicare database, patients receiving ADT had significantly higher rates of fracture compared with patients who did not receive ADT (19.4% vs. 12.6%).[9] Although these rates of fragility fractures are lower than skeletal-related events in patients with metastatic disease (as described below), the population at risk includes patients with metastatic disease as well as patients with localized disease receiving ADT in conjunction with radiation therapy. Thus, fracture prevention for men receiving ADT is an important opportunity for intervention.

Osteoclast-Targeted Therapies

Osteoclast inhibition has been shown to be therapeutically beneficial for men with prostate cancer in 2 specific clinical settings. It can decrease the incidence of skeletal events because of metastatic CRPC and can reduce the incidence of fragility fractures caused by ADT-induced osteoporosis. Osteoclast inhibition can be accomplished with bisphosphonates or the monoclonal antibody denosumab. Additional potential targets of osteoclast signaling in prostate cancer (eg, Src tyrosine kinase, integrins, matrix metal-loproteinases) that are in preclinical or early-stage clinical development are not the focus of this review.

Bisphosphonates

Bisphosphonates can directly inhibit the recruitment and differentiation of osteoclast precursors, and the attachment and survival of established osteoclasts.[27] Bisphosphonates are synthetic analogs of pyrophosphate, a normal component of bone matrix, and thereby bind to areas of exposed hydroxyapatite crystals, diminishing the availability of those crystals for osteoclast-mediated resorption. Bisphosphonates can also indirectly inhibit osteoclast differentiation and activation via effects on osteoblasts.[27] Bisphosphonates can affect prostate cancer survival and inhibit RANKL expression by cancer cells, which may further diminish osteoclast activity.[28]

The R2 side chain determines the potency of bisphosphonates. Pamidronate and others with a primary amino group at R2 are more potent than non-amino-group containing compounds,

such as clodronate or etidronate. The most potent bisphosphonates, including ZA, contain a secondary or tertiary amino group; correspondingly, ZA is 100 times more potent than pamidronate, and at least 1000 times more potent than etidronate in vitro.

Bisphosphonates are an important treatment for patients with bone metastases. In 1995, pamidronate was approved to treat patients with multiple myeloma or metastatic breast cancer based on randomized controlled trials demonstrating that pamidronate decreased risk of skeletal complications.[29,30] In 2002, intravenous (I.V.) ZA was approved to treat patients with multiple myeloma and bone metastases from any solid tumor, including prostate cancer, based on the results of 3 randomized controlled trials involving more than 3000 patients.[31-33]

The role of bisphosphonates in the prevention of metastasis is unclear. In animal models of breast cancer, ZA treatment significantly reduced the number of bone and visceral metastases compared with controls.[34] In a randomized trial of 302 women with primary breast cancer considered to be at high risk for bone metastasis, 2 years of oral adjuvant clodronate was associated with a significantly lower incidence of osseous and visceral metastases, as well as fewer bone metastases per patient.[35] However, subsequent similarly designed studies in breast cancer patients failed to demonstrate a significant reduction in the occurrence of bone metastasis with adjuvant clodronate, although the inclusion criteria were slightly different.[36,37] In a recent report of the ABCSG-12 trial, the addition of ZA to adjuvant endocrine therapy in localized breast cancer patients resulted in a 36% relative reduction of the risk of disease relapse.[38] Additional ongoing phase III trials in breast cancer will examine whether the addition of bisphosphonates to adjuvant therapy affects disease-free survival (NSABP B-34, BIG 1-04 AZURE). In prostate cancer, the role of bisphosphonates in the prevention of metastasis remains undefined.

Denosumab

Denosumab (AMG 162, Amgen Inc., Thousand Oaks, CA) is a fully human monoclonal IgG_2 antibody with an extremely high affinity for human RANKL (Kd approximately 10^{-12} M).[39] Unlike the bisphosphonates, denosumab has a long circulatory half-life (> 30 days) and does not accumulate in bone. Denosumab has been examined in a variety of clinical settings including postmenopausal osteoporosis, rheumatoid arthritis, breast cancer, multiple myeloma, prostate cancer, and other solid tumors. In postmenopausal women, 1 dose of denosumab caused rapid (within 12 hours), marked (> 80%), and sustained (6 month) suppression of osteoclast activity.[40] The drug also achieved rapid, sustained suppression of osteoclast activity in patients with multiple myeloma or bone metastasis from breast cancer.[41,42]

Osteoprotegerin

As endogenous OPG is a decoy receptor for RANKL, recombinant OPG has been investigated as a therapeutic strategy to inhibit RANKL. Though recombinant OPG showed early-phase promise for the treatment of postmenopausal osteoporosis, multiple myeloma, and metastatic breast cancer,[43,44] it was less potent than denosumab[43] and carries theoretical risks for (1) triggering antibodies that are cross-reactive against endogenous OPG, and (2) interference with the tumor suppressive function of TNF-related apoptosis-inducing ligand (TRAIL).[43] Recombinant OPG is therefore no longer in clinical development.

Clinical Settings for Osteoclast-Targeted Therapies

There are 4 distinct clinical situations in which inhibition of osteoclast activity may be beneficial for men with prostate cancer. First, men with CRPC and bone metastases are at increased risk for skeletal-related events (SREs; includes pathologic fracture, need for

radiation therapy or surgery to bone, spinal cord compression). Second, men with castration-sensitive prostate cancer metastatic to bone are also at increased risk for SREs. Studies involving the first two clinical scenarios are summarized in Table 1. Third, men with CRPC but no bone metastases are at high risk for the development of bone metastases (Table 2). Finally, men receiving ADT for any reason are at increased risk for fragility fractures (Table 3). Ongoing and completed clinical trials have examined the abilities of osteoclast-targeted therapies to reduce these 4 types of risk.

Metastatic Castration-Resistant Prostate Cancer

Three randomized controlled trials have evaluated the role of bisphosphonates for patients with bone metastases because of CRPC. Taken together, these trials established ZA as the Food and Drug Administration (FDA)-approved standard-of-care for the prevention of SREs in this patient population. More recently, denosumab was superior to ZA in a phase III clinical trial in this clinical setting, and may become the new standard-of-care.

The Zometa 039 Trial

Zoledronic acid was FDA approved to treat men with bone-metastatic prostate cancer and disease progression despite first-line hormonal therapy, based on the results of the Zometa 039 trial. In this trial, 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases were assigned randomly to I.V. ZA (4 or 8 mg every 3 weeks) or placebo.[33] All men continued ADT and received additional cancer therapy at the discretion of the treating physicians. The primary study endpoint was the proportion of men who experienced 1 or more SRE (pathologic fracture, spinal cord compression, surgery or radiation therapy to bone, or change in antineoplastic treatment to treat bone pain) by 15 months.

The study was amended because of adverse renal events (grade 3 increases in serum creatinine). First, ZA was infused over a longer time period (from 5 to 15 minutes) and in greater infusate volume (from 50 to 100 mL). Second, the ZA 8 mg treatment dose was reduced to 4 mg, with serum creatinine monitoring before each dose, and the primary efficacy assessment became the comparison of the 4 mg group versus placebo. After these amendments, adverse renal events between the groups were similar.

Zoledronic acid was associated with fewer SREs than the placebo group at 15 months (33.2% vs. 44.2%; $P = .021$). Zoledronic acid increased the median time to first SRE (488 days vs. 321 days; $P = .009$).[45] Although median survival was longer in the ZA group than in the placebo group (546 days vs. 464 days; $P = .091$), the study was not designed to evaluate the effect of ZA on survival, and the observed difference in overall survival (OS) was not statistically significant.

CGP 032/INT 05

Intravenous pamidronate was examined in men with CRPC and symptomatic bone metastases in 2 similarly designed, multicenter trials, CGP 032 and INT 05, which were pooled and reported together. A total of 350 men were assigned randomly to either pamidronate 90 mg or placebo every 3 weeks for 27 weeks.[46] Primary endpoints were self-reported pain, analgesic use, and SREs (defined as pathologic fracture, radiation or surgery to bone, spinal cord compression, or hypercalcemia). Neither the primary endpoints nor survival differed between the groups.

The negative results may have been due to less potent suppression of osteoclast activity, inclusion of subjects with more advanced disease, and use of less precise study endpoints. For example, pamidronate decreased urinary NTx markers of osteoclast activity by

approximately 50%, whereas ZA decreases urinary markers of osteoclast activity by 70%-80%.[33]

NCIC CTG PR.6

Intravenous clodronate was evaluated in 209 men with symptomatic, bone-metastatic CRPC who concurrently received mitoxantrone (12 mg/m^2 intravenously every 3 weeks) and prednisone, in the National Cancer Institute of Canada Clinical Trials Group PR.6 study. Patients receiving mitoxantrone and prednisone were randomly assigned to receive either clodronate (1500 mg every 3 weeks) or placebo.[47] The primary endpoint was palliative response, defined as a 2-point decrease in the pain index (or reduction to zero) or a 50% decrease in analgesic intake, without increase in the other outcome. Palliative responses were similar between the clodronate arm (46% of 104 patients) and the placebo arm (39% of 105 patients; $P = .54$). The 2 groups were similar when evaluated for median duration of response, symptomatic disease progression-free survival (PFS), OS, and overall quality of life. Subgroup analysis suggested a possible benefit in men with more severe pain.

Zometa 039, CGP 032/INT 05, and NCIC CTG PR.6 show that ZA, but not the other less-potent bisphosphonates, decreases the risk of skeletal complications in men with CRPC and bone metastases.

Denosumab Protocol 20050103

RANK ligand inhibition in CRPC and bone metastases has been examined in Amgen Inc., protocol 20050103 (NCT 00321620), a randomized, double-blind multicenter study. A total of 1901 patients were randomly assigned to denosumab (120 mg subcutaneously every 4 weeks) or ZA (4 mg intravenously every 4 weeks). The primary endpoint was time to first on-study SRE (pathologic fracture, radiation to bone, surgery to bone, or spinal cord compression). The primary objective was to demonstrate non-inferiority of denosumab compared with ZA. Secondary objectives evaluated superiority of denosumab and comparative safety and tolerability of the 2 drugs.

Denosumab was superior to ZA in delaying the time to first on-study SRE (HR, 0.82; 95% CI, 0.71-0.95) and reducing rates of multiple SREs (HR, 0.82; 95% CI, 0.71-0.94).[48] The groups were similar with regard to OS and time to disease progression. Adverse event rates were similar, without a significant difference in osteone-crosis of the jaw (22 in the denosumab arm and 12 in the ZA arm). Based on these results, denosumab may become the new standard of care for prevention of SREs in men with CRPC.

Castration-Sensitive Metastatic Prostate Cancer

Only 1 completed randomized controlled trial has evaluated bisphosphonate treatment among men with metastatic prostate cancer who are responding to first-line ADT. In that study, MRC PR05, clodronate failed to produce benefit. CALGB/CTSU 90202 is an ongoing study that will evaluate ZA for this application.

MRC PR05

The Medical Research Council PR05 study included 311 men with prostate and bone metastases who were either initiating or responding to primary ADT. Participants were randomized to either oral clodronate (2080 mg daily) or placebo in addition to continued ADT.[49] The primary endpoint was symptomatic skeletal disease progression or prostate cancer death. Overall survival was a secondary endpoint. After a median follow-up of 59 months, the clodronate group had nonsignificant improvements in bone PFS (HR, 0.79; 95% CI, 0.61-1.02; $P = .066$) and OS (HR, 0.80; 95% CI 0.62-1.03; $P = .082$). Long-term OS

data after 258 deaths revealed a significant benefit in the clodronate group compared with placebo (8-year OS, 22% vs. 14%; HR, 0.77; 95% CI, 0.60-0.98; $P = .032$).[50] As the survival benefit of early use of clodronate in castration-sensitive metastatic disease has only recently been reported, the clinical effect of this study is as yet unknown.

CALGB/CTSU 90202

CALGB/CTSU 90202 (NCT00079001) is an ongoing randomized controlled trial that is designed to clarify the role of ZA in castration-sensitive metastatic prostate cancer. Enrollment includes 680 men with prostate cancer and bone metastases who have recently initiated ADT. Participants are randomized to ZA (4 mg intravenously every 4 weeks) or placebo. The primary endpoint is SRE or prostate cancer death. Crossover to open-label zoledronic acid is prompted by either progression to castration-resistant disease or first SRE. Accrual is ongoing.

Prevention of Bone Metastasis in Nonmetastatic Prostate Cancer

There is currently no evidence that osteoclast-targeted therapy prevents the development of bone metastasis. Randomized controlled trials with clodronate and with ZA have failed to show that a bisphosphonate can prevent or delay the development of bone metastases in those who do not yet have bone metastases. Denosumab is currently under study for the prevention of metastases in a large phase III randomized placebo-controlled trial.

MRC PR04

The MRC PR04 trial evaluated clodronate for the prevention of symptomatic bone metastases in patients considered to be at high risk. Enrollment included 508 men receiving treatment for localized T2-T4 prostate cancer with no evidence of bone metastases.[51] Participants were randomized to 5 years of treatment with oral clodronate (2080 mg daily) or placebo. Most patients were treated with standard-of-care external-beam radiation therapy, external-beam radiation therapy with hormone therapy, or primary hormone therapy. The primary endpoint was time to development of symptomatic bone metastases or prostate cancer death. There was no significant difference between the groups after a median of 10 years of follow-up and a total of 148 events. Overall survival at 5-years was 78% for the entire study population. Prostate cancer death event rates were similar in both groups (HR, 1.07; 95% CI, 0.76-1.49; $P = .71$). There was also no difference in OS between the groups in long-term follow-up (281 deaths; HR, 1.12; 95% CI, 0.89-1.42; $P = .94$). These results contrast with the survival benefit seen with clodronate in castration-sensitive metastatic disease (MRC PR05, described above).[50]

Zometa 704

The Zometa 704 trial was designed to evaluate the ability of ZA to affect time to first bone metastasis in men with nonmetastatic CRPC. Enrollment included prostate cancer patients with prostate-specific antigen (PSA) progression despite ADT but no radiographic evidence of metastases. Participants were randomized to ZA (4 mg intravenously every 4 weeks) or placebo and were evaluated with a bone scan every 4 months. The primary endpoint was time to first bone metastasis. Target accrual was 991.

The Data and Safety Monitoring Board terminated the study after enrollment of 398 patients because the observed event rate was lower than expected. The low event rate and early termination of the study prevent adequate evaluation of efficacy. Time to first bone metastasis was similar for both groups.

Examination of the placebo group from this study has helped characterize the natural history of a rising PSA in men with castrate nonmetastatic prostate cancer.[52] At 2 years, one third of patients had developed bone metastases. Median bone metastasis–free survival was 30 months. Median time to first bone metastasis and OS were not reached. Baseline PSA and PSA velocity independently predicted shorter time to first bone metastasis, metastasis-free survival, and OS. Other factors did not consistently predict clinical outcomes. These observations have helped to identify men at high risk for development of bone metastases and have informed the design of subsequent clinical trials.

ZEUS

The Zometa European Study (ZEUS) is a current, open-label, randomized, controlled trial that will evaluate the ability of ZA to prevent bone metastasis in men with high-risk prostate cancer.[53] Eligibility requires at least 1 high-risk prognostic factor: PSA ≥ 20 ng/mL, lymph node–positive disease, or Gleason sum of 8-10. As of 2008, 1433 patients were randomized to standard prostate cancer therapy with or without ZA (4 mg intravenously every 3 months for 48 months). The primary objective is to demonstrate superiority of ZA in the proportion of patients with at least 1 bone metastasis after 48 months of treatment. Secondary objectives will evaluate the effects of ZA on OS, symptomatic disease progression, PSA doubling time, and biochemical markers of bone turnover. The study is ongoing.

Denosumab Protocol 20050147

Amgen protocol 20050147 (NCT 00286091) is an ongoing trial that has accrued 1435 men with prostate cancer, no bone metastases, and rising PSA despite current ADT. Enrollment was limited to patients at high risk for development of bone metastases based on PSA doubling time ≤ 10 months and/or PSA ≥ 8 ng/dL. Participants were randomly assigned to denosumab (120 mg subcutaneously every 4 weeks) or placebo. The primary endpoint is bone metastasis–free survival. Final study results are expected in 2010.

Treatment-Related Fragility Fractures

Androgen deprivation causes accelerated loss of BMD and is associated with increased risk for fragility fractures. Multiple bisphosphonates improve BMD in men receiving ADT, including alendronate,[54] pamidronate,[25,55] ZA,[56,57] and neridronate.[58] Selective estrogen receptor modulators (SERMs) such as raloxifene[59] and toremifene[60] have also been shown to improve BMD in this clinical setting. Although BMD is correlated with fracture risk, it is a surrogate rather than clinical endpoint. The National Osteoporosis Foundation (NOF) recommends fracture risk assessment with the World Health Organization (WHO)/Fracture Risk Assessment (FRAX) tool, which is based on epidemiologic data from the general population. Given that men who receive ADT for prostate cancer are vulnerable to fragility fractures, FRAX was applied to 363 prostate cancer patients on ADT.[61] Using clinical risk factors in the algorithm, the prevalence of risk sufficient to initiate drug therapy was high (51.2% of all patients) and was strongly influenced by age (3.3% in men younger than 70 years, 76.6% in those 70-79 years old, and 98.8% in those 80 years of age or older). The FRAX algorithm identified a greater proportion of men above the fracture risk threshold for treatment than the traditional BMD definition of osteoporosis (T score −2.5 or less). The free online FRAX calculator (http://www.shef.ac.uk/FRAX/) allows for the rapid identification of patients at risk for fragility fractures.

No bisphosphonate trial has been adequately powered to demonstrate a reduction in the risk for treatment-associated clinical fractures among men receiving ADT. Two positive phase III fracture-prevention trials have recently been reported. Denosumab and toremifene have

each been shown to significantly reduce fracture risk in this vulnerable population and are likely to alter clinical practice.

Denosumab HALT 138

Denosumab protocol 20040138 (HALT 138) enrolled 1468 men receiving ADT and at particularly elevated fracture risk from previous history of osteoporotic fracture, low baseline BMD, or age ≥ 70 years.[62] Participants were randomized to 3 years of treatment with either denosumab (60 mg subcutaneously every 6 months) or placebo. The primary endpoint was percent change in BMD in the lumbar spine. Secondary endpoints were change in BMD at other sites and incidence of new vertebral fractures. Denosumab significantly increased BMD of the lumbar spine (6.7%), total hip (4.8%), femoral neck (3.9%), and distal third of radius (5.5%). Denosumab also reduced the 3-year incidence of new vertebral fractures by 62% (relative risk, 0.38; 95% CI, 0.19-0.78; $P = .006$). Fractures at any site were reduced by 28% in the denosumab group ($P = .10$). Multiple fractures were reduced by 72% ($P = .006$). Incidence of adverse events was similar in the denosumab and placebo groups.

Toremifene Protocol G300203

Toremifene protocol G300203 (NCT00129142) enrolled 1389 men receiving ADT who were at particularly elevated risk for fracture because of low BMD or age ≥ 70 years.[63] Participants were randomized to 2 years of treatment with either toremifene (80 mg by mouth daily) or placebo. Incidence of morphometric vertebral fractures was the primary endpoint. Secondary endpoints included BMD at the hip, BMD at the lumbar spine, breast pain, hot flashes, and lipid profile.

Toremifene significantly reduced the number of new vertebral fractures when compared with placebo (2.5% vs. 4.9%; RR, 0.50; $P < .05$). Toremifene also significantly increased BMD at the lumbar spine by 2% and at the hip by 1.6%. It decreased breast pain, decreased hot flashes, and caused favorable changes in lipid profile (ie, increased high-density lipoprotein and decreased low-density lipoprotein and triglycerides).

Conclusion

Bone metastases and skeletal complications cause substantial morbidity in men with advanced prostate cancer. Currently available evidence supports the use of ZA (4 mg every 3-4 weeks) to reduce skeletal-related events in men with CRPC and bone metastases. Less-potent bisphosphonates failed to significantly reduce SREs in similar studies. Optimal timing, schedule, and duration of bisphosphonate treatment in men with bone metastases have not been well defined.

RANKL signaling plays a central role in bone-metastatic disease caused by prostate cancer and other diseases (breast cancer, osteoporosis, multiple myeloma). Denosumab, the monoclonal antibody to RANKL, was superior to ZA for the management of bone-metastatic CRPC. Denosumab has also been shown to prevent ADT-associated fragility fractures in men without metastases to bone. Toremifene, a SERM, also significantly decreases fracture risk in patients receiving ADT. Metastasis prevention is an unmet medical need and is the subject of ongoing phase III clinical trials.

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Table 1

Randomized Controlled Trials of Osteoclast-Targeted Therapies in Prostate Cancer Metastatic to Bone

Study	Number of Patients	Study Population	Arms	Outcome
Zometa 039[33,45]	643	Castration-resistant, asymptomatic or minimally symptomatic	4 mg zoledronic acid versus placebo, every 3 weeks for 15 months	Significant decrease in SREs (33.2% vs. 44.2%); trend toward improved survival; established zoledronic acid as standard of care in this setting
CGP 032/INT 05[46]	350	Castration-resistant, symptomatic	90 mg pamidronate versus placebo, every 3 weeks for 27 weeks	No significant difference in pain, analgesic use, or SREs
NCIC CTG Pr.6[47]	209	Castration-resistant, symptomatic	Mitoxantrone and prednisone ± 1500 mg clodronate, every 3 weeks until progression	No significant difference in palliative response, duration of response, progression-free survival, overall survival, overall quality of life
Denosumab protocol 20050103[48]	1901	Castration-resistant	120 mg denosumab versus 4 mg zoledronic acid, every 4 weeks	Denosumab was superior to zoledronic acid; no difference in overall survival or adverse event rates
MRC PR05[49,50]	311	Castration-sensitive	2080 mg daily oral clodronate versus placebo, for 3 years maximum	Trend toward improved bone progression-free survival (P = .066); significantly improved 8-year overall survival (22% vs. 14%; HR, 0.077; P = .032)
CALGB/CTSU 90202	680[a]	Castration-sensitive	4 mg zoledronic acid versus placebo, every 4 weeks until progression to CRPC or first SRE, then cross over to open label	Ongoing Primary endpoint: SRE or prostate cancer death

[a]Targeted accrual.

Abbreviations: CRPC = castrate-resistant prostate cancer; SRE = skeletal-related events

Table 2

Randomized Controlled Trials of Osteoclast-Targeted Therapies in Prevention of Bone Metastasis in Nonmetastatic Prostate Cancer

Study	Number of Patients	Study Population	Arms	Outcome
MRC PR04[51]	508	Castration-sensitive, localized, clinical stage T2-T4	2080 mg daily oral clodronate versus placebo, for 5 years	No difference in development of bone metastasis or overall survival
ZEUS[53]	1433	Castration-sensitive, high-risk disease (PSA ≥ 20, lymph node-positive disease, or Gleason sum 8-10)	Standard prostate cancer therapy ± zoledronic acid 4 mg intravenously every 3 months for 48 months (open label)	Ongoing Primary objective: evaluate superiority of zoledronic acid over control in incidence of bone metastasis
Denosumab Protocol 20050147	1400[a]	Castration-resistant, high risk by PSA criteria	Denosumab 120 mg versus placebo, every 4 weeks	Ongoing Primary endpoint: bone metastasis-free survival Final results expected, 2010

[a]Targeted accrual.

Abbreviation: PSA = prostate-specific antigen

Table 3
Randomized Controlled Trials of Fracture Prevention in Prostate Cancer

Study	Number of Patients	Study Population	Arms	Outcome
Denosumab HALT 138[62]	1468	Castration-sensitive, current androgen-deprivation therapy; no metastases; high risk for fracture	Denosumab 60 mg versus placebo, every 6 months for 3 years	Significant increase in bone mineral density; significant 62% reduction in 3-year incidence of new vertebral fractures
Toremifene Protocol G300203[63]	1389	Castration-sensitive, current androgen-deprivation therapy; high risk for fracture	Toremifene 80 mg daily oral versus placebo	Fewer new vertebral fractures (2.5% vs. 4.9%; $P < .05$); increased bone mineral density, decreased breast pain, decreased hot flashes, favorable lipid profile changes