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Treatment and prevention of bone complications from prostate cancer

Richard J. Lee, M.D., Ph.D., **Philip J. Saylor, M.D.**, and **Matthew R. Smith, M.D., Ph.D**
Department of Oncology, Massachusetts General Hospital Cancer Center, Boston, MA

Abstract

Bone metastases and skeletal complications are major causes of morbidity in prostate cancer patients. Despite the osteoblastic appearance of bone metastases on imaging studies, patients have elevated serum and urinary markers of bone resorption, indicative of high osteoclast activity. Increased osteoclast activity is independently associated with higher risk of subsequent skeletal complications, disease progression, and death. Osteoclast-targeted therapies are therefore a rational approach to reduction of risk for disease-related skeletal complications, bone metastases, and treatment-related fractures. This review focuses on recent advances in osteoclast-targeted therapy in prostate cancer. Bisphosphonates have been extensively studied in men with prostate cancer. Zoledronic acid significantly decreased the risk of skeletal complications in men with castration-resistant prostate cancer and bone metastases, and is FDA-approved for this indication. Denosumab is a human monoclonal antibody that binds and inactivates RANKL, a critical mediator of osteoclast differentiation, activation, and survival. Recent global phase 3 clinic trials demonstrated an emerging role for denosumab in the treatment of prostate cancer bone metastases and prevention of fractures associated with androgen deprivation therapy.

Keywords

bisphosphonate; denosumab; metastasis; osteoclast; prostate cancer; RANKL; toremifene; zoledronic acid

Clinical manifestations of bone complications in prostate cancer

The American Cancer Society estimates for 2009 included over 192,000 new cases of prostate cancer in the United States, accounting for 25% of cancer diagnoses in men, and over 27,000 deaths from metastatic disease[1]. The major site of hematogenous spread of prostate cancer is bone, seen in 80-90% of men with castration-resistant metastatic prostate cancer undergoing therapy[2,3], and 90% of patients at autopsy[4]. The most common sites of bone metastasis are the vertebral column, pelvis, ribs, long bones, and skull. These are

Corresponding author: Richard J. Lee, M.D., Ph.D., Instructor in Medicine, Harvard Medical School, Massachusetts General Hospital Cancer Center, 55 Fruit Street, Yawkey 7E, Boston, MA 02114, Tel: 617.724.4000, Fax: 617.643.1740, rjlee@partners.org.

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areas of active hematopoiesis in adults and are hypothesized to provide tumor cells with a rich growth environment. Unlike other cancers that commonly metastasize to bone and cause osteolytic lesions, prostate cancer causes predominantly osteoblastic lesions.

Bone metastases from prostate cancer are a major cause of morbidity. Pain is the most common symptom. Vertebral metastases may cause compression fractures, spinal cord compression, nerve root compression, and cauda equina syndrome. Pathologic fractures of proximal long bones occur at lower rates compared with vertebral fractures[5]. Hypocalcemia, as a result of excessive bone formation, and subsequent secondary hyperparathyroidism is common[6]. Ineffective erythropoiesis due to bone metastases and cancer therapies contributes to a high prevalence of anemia among men with advanced prostate cancer.

Fragility fractures due to osteoporosis are common in older men[7]. The common risk factors for developing osteoporosis in men include hypogonadism, chronic glucocorticoid therapy, and excessive alcohol intake[8]. Androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) agonist is the standard initial hormonal treatment for metastatic prostate cancer. ADT causes severe hypogonadism and significantly increases the risk of fracture [9,10]. Thus, the biology and treatment of advanced prostate cancer cause important changes in bone integrity with significant clinical consequences. Opportunities for therapeutic intervention and clinical trial data on the treatment and prevention of bone complications from prostate cancer are reviewed here.

Normal bone physiology

In adults, normal bone homeostasis is the product of constant remodeling, maintained by a balance of formation by osteoblasts and resorption by osteoclasts. Osteoclasts arise from the monocyte lineage. Osteoclasts are activated by local and systemic factors to resorb bone during normal bone remodeling and in pathologic states. Bone resorption by activated osteoclasts is accomplished by the release of proteases that dissolve the matrix. This process releases immobilized growth factors, further enriching the marrow's growth factor milieu[11,12].

RANK signaling plays a central role in osteoclast differentiation, activation, and survival. Osteoclasts express receptor activator of nuclear factor-κB (RANK), a member of the tumor necrosis factor (TNF) receptor superfamily. RANK is activated by RANK ligand (RANKL). RANK expression is required for osteoclast differentiation and activation. RANKL is expressed by bone marrow stromal cells (also called mesenchymal stem cells) and osteoblasts, and the binding of RANKL to RANK induces the differentiation of osteoclasts from their precursors. Osteoprotegerin (OPG) is a decoy receptor for RANKL, and thereby protects bone from resorption[13]. OPG is expressed by osteoblasts and other tissues, and is itself a member of the TNF receptor superfamily. The ratio of RANKL to OPG regulates the activity of osteoclasts. Animal studies highlight the importance of the RANKL/OPG ratio: overexpression of OPG in transgenic mice causes osteopetrosis[14], whereas targeted deletion of OPG causes osteopenia[15].

Pathophysiology of bone metastasis from prostate cancer

Numerous factors may account for the propensity for cancer to metastasize to bone, including high blood flow to bone marrow, a rich growth factor milieu in areas of active hematopoiesis, and a large repository of immobilized growth factors in the matrix[12]. Despite having a dense radiographic appearance, the woven bone of osteoblastic metastases from prostate cancer is structurally weak and associated with increased fracture risk[16].

Osteoclast number and activity are increased in osteoblastic metastases and in adjacent bone, consistent with the high turnover state of prostate cancer bone metastasis[5,16,17]. Markers of bone resorption, such as urine N-telopeptide (NTx) and bone-specific alkaline phosphatase, are higher in patients with bone metastasis compared to those without, indicative of elevated bone turnover despite the osteoblastic radiographic appearance[18,19]. Increased osteoclast activity is independently associated with risk for subsequent skeletal complications, disease progression, and death[5,20]. These studies underscore the contribution of cancer-mediated osteoclast activation to the clinical complications of metastatic disease.

Parathyroid hormone (PTH) stimulates osteoclast formation by inducing RANKL expression in bone marrow stromal cells and osteoblasts. Hypocalcemia caused by osteoblast-driven calcium-phosphate deposition may stimulate PTH production, with resultant secondary hyperparathyroidism. This creates a vicious cycle of osteoclast activation, growth factor liberation from the bone matrix, tumor cell proliferation in the bone, osteoblast activation, calcium-phosphate deposition, and secondary hyperparathyroidism.

Osteoclast modulation has been examined in animal models. In a murine model of prostate cancer, inhibition of osteoclast activity by zoledronic acid did not inhibit the development of osteoblastic metastases[21]. Therefore, an unanswered question in bone metastasis biology is whether bone resorption precedes osteoblastic metastatic development or is a consequence of increased bone formation.

Osteoblast activity is another rational target for therapeutic inhibition in prostate cancer. Atrasentan is an investigational agent that inhibits the endothelin receptor A, resulting in decreased osteoblast activity. The development of atrasentan and other endothelin antagonists in prostate cancer is reviewed elsewhere[22].

Pathophysiology of prostate cancer therapy-induced osteoporosis

Therapy for prostate cancer influences osteoclast activity. Androgen deprivation therapy (ADT) is the cornerstone of treatment for metastatic prostate cancer. ADT is also a routine part of the management for many men with intermediate or high risk, early stage prostate cancer undergoing radiation therapy, as well as those with recurrent disease following surgery or radiation therapy for early stage disease. ADT can be accomplished by either bilateral orchiectomies or chronic therapy with a GnRH agonist or antagonist. The intended therapeutic effect of ADT is severe hypogonadism. Although castrate testosterone has traditionally been defined as a serum testosterone level of less than 50 ng/mL, modern assays have shown that surgical or medical castration generally lowers serum testosterone to under 20ng/mL[23,24].

The profound hypogonadal state is associated with metabolic changes including decreased bone mineral density (BMD)[25]. ADT with GnRH agonists increases PTHmediated osteoclast activation, as well as biochemical markers of osteoblast and osteoclast activity[26,27]. In prostate cancer patients, ADT raises the risk of fracture[9,10]. In a review of over 50,000 patients in the Surveillance, Epidemiology, and End Results (SEER) program and Medicare database, 19.4% of patients who received ADT experienced a fracture compared with 12.6% in those who did not receive ADT[10]. Fracture prevention strategies for those at high risk for fragility fractures are important opportunities for intervention.

Osteoclast-targeted therapies

Several commercially available and investigational agents inhibit osteoclast function, leading to decreased bone resorption and potentially less skeletal morbidity due to metastatic

prostate cancer or ADT-induced osteoporosis. Most of these agents have also been explored as treatments for osteoporosis or for other neoplasms that spread to bone. Other potential targets of osteoclast signaling in prostate cancer (*e.g.*, Src tyrosine kinase, integrins, matrix metalloproteinases) that are in preclinical or early stage clinical development will not be reviewed here.

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate, a normal component of bone matrix. They bind to areas of exposed bone mineral and are rapidly cleared from the circulation. By binding hydroxyapatite crystals, bisphosphonates diminish the availability of those crystals for osteoclast-mediated resorption. Bisphosphonates can directly inhibit the activities of osteoclasts and their precursors, including recruitment, differentiation, attachment, and survival[28]. Bisphosphonates indirectly inhibit osteoclast differentiation and activation via effects on osteoblasts[28]. Bisphosphonates can induce apoptosis and inhibit RANKL expression in prostate cancer cells, which may further diminish osteoclast activity[29].

The potency of bisphosphonates is determined by the R2 side chain. Those that contain a primary amino group at R2 (*e.g.*, pamidronate) are more potent than nonamino-group containing bisphosphonates, such as clodronate or etidronate. The most potent bisphosphonates, including zoledronic acid, contain a secondary or tertiary amino group, with activity 100 times more potent than clodronate or pamidronate, and at least 1000 times more potent than etidronate.

Bisphosphonates are an established and important component of care for patients with bone metastasis. In 1995, intravenous pamidronate was approved to treat patients with multiple myeloma or metastatic breast cancer based on evidence from randomized controlled trials that pamidronate decreases risk of skeletal complications[30,31]. In 2002, intravenous zoledronic acid was approved to treat patients with multiple myeloma and bone metastases from any solid tumor including prostate cancer. This approval was based on the results of three randomized controlled trials involving more than 3000 patients[32-34].

The ability of bisphosphonates to delay the appearance and progression of visceral and skeletal metastasis is unclear. Preclinical data in mouse models of metastatic breast cancer indicate a significant reduction in bone and visceral metastases with zoledronic acid treatment[35]. Diel *et al.* randomized 302 women with primary breast cancer considered to be at high risk for bone metastasis (due to the presence of tumor cells in the bone marrow) to receive oral adjuvant clodronate or standard follow-up, for two years[36]. Patients who received clodronate had a significantly lower incidence of osseous and visceral metastases, as well as fewer bone metastases per patient. However, subsequent similarly-designed studies failed to demonstrate a significant reduction in the occurrence of bone metastasis with adjuvant clodronate in breast cancer patients, although the inclusion criteria were slightly different[37,38]. The addition of zoledronic acid to adjuvant endocrine therapy in localized breast cancer patients resulted in a 36% relative reduction of the risk of disease progression (the ABCSG-12 trial)[39]. Additional ongoing phase III trials in breast cancer will examine the effect of the addition of bisphosphonates to adjuvant therapy on disease-free survival (NSABP B-34, BIG 1-04 AZURE). The role of bisphosphonates, especially the more potent amino-bisphosphonates, in prevention of metastasis in prostate cancer patients remains undefined.

Denosumab

Denosumab (AMG 162, Amgen Inc., Thousand Oaks, California) is a fully human monoclonal IgG_2 antibody directed against RANKL, with an extremely high affinity for human RANKL (Kd approximately 10^{-12} M)[40]. In contrast to bisphosphonates, denosumab does not accumulate in bone and has a long circulatory half life (>30 days). Denosumab has been examined in post-menopausal osteoporosis, rheumatoid arthritis, multiple myeloma, breast cancer, prostate cancer, and other solid tumors. In postmenopausal women, a single administration of denosumab resulted in rapid (within 12 hours), marked (>80%), and sustained (6 month) suppression of osteoclast activity[41]. In patients with multiple myeloma or bone metastasis from breast cancer, denosumab was well-tolerated and achieved rapid and sustained suppression of osteoclast activity[42,43].

Osteoprotegerin

RANKL inhibition using recombinant osteoprotegerin has also been tested. The Fc portion of the immunoglobulin heavy chain was fused to the amino-terminus of OPG to generate recombinant Fc-OPG. In postmenopausal women with osteoporosis, Fc-OPG decreased markers of osteoclast activity by 80% after four days, with significant effects lasting 45 days; markers of osteoblast activity were not changed[44]. No serious adverse effects were reported. A different formulation of OPG, AMGN-0007, was examined in patients with multiple myeloma or breast cancer with lytic bone lesions[45]. AMGN-0007 was well-tolerated and exhibited comparable effects on bone metabolism to pamidronate.

When the two forms of RANKL inhibition were compared, denosumab was more potent than recombinant OPG, with greater decreases in bone turnover markers and longer duration of action[44]. Further, two theoretical risks inherent to recombinant OPG are not applicable to denosumab: (1) the generation of anti-Fc-OPG antibodies which may cross-react and interfere with endogenous OPG function, and (2) the binding of OPG to TNF-related apoptosis-inducing ligand (TRAIL), which may interfere with its role in the normal defense mechanism against tumorigenesis[44]. Despite its promise, recombinant OPG has therefore given way to denosumab in strategies to inhibit RANKL activity and osteoclast activation.

Clinical settings for osteoclast-targeted therapies

How does inhibition of osteoclast activity and bone remodeling influence disease progression? Four common clinical questions have been studied. (1) Does inhibition of bone remodeling reduce skeletal-related events (SREs; includes pathologic fracture, need for radiation therapy or surgery to bone, spinal cord compression) in prostate cancer patients with bone metastases and castration-resistant disease? (2) Can SREs be reduced in patients with bone metastases and castration-sensitive disease? (3) Does osteoclast-targeted therapy prolong bone metastasis-free survival in men with castration-resistant disease and no bone metastases at baseline? (4) Can such therapies reduce fracture rates due to ADT-induced osteoporosis? The clinical trials addressing these questions are presented below and are summarized in tables 1-3.

Metastatic castration-resistant prostate cancer

Three contemporary randomized controlled trials have evaluated the efficacy of bisphosphonates for patients with bone metastases and disease progression despite first-line hormonal therapy (castration). One recently completed study compared denosumab with zoledronic acid in this setting. These patients are contemporarily described as having castration-resistant prostate cancer (CRPC, previously termed “hormone-refractory prostate cancer”). At present, zoledronic acid is the Food and Drug Administration (FDA)-approved

standard of care for the prevention of SREs in this patient population. The demonstrated superiority of denosumab over zoledronic acid may alter this standard.

Zometa 039

In the Zometa 039 study, 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases were assigned randomly to intravenous zoledronic acid (4 or 8 mg every 3 weeks) or placebo[34]. All men continued ADT (bilateral orchiectomies or treatment with a GnRH agonist) throughout the study and received additional antineoplastic therapy at the discretion of the treating physicians. The primary study endpoint was the proportion of men who experienced one or more SRE (pathological fracture, spinal cord compression, surgery or radiation therapy to bone, or change in antineoplastic treatment to treat bone pain) by 15 months.

Adverse renal events (grade 3 increases in serum creatinine) prompted two study amendments. First, the infusion time for zoledronic acid was increased from 5 to 15 minutes, with an increase in infusate volume from 50 to 100 mL. Second, the zoledronic acid dose in the 8 mg treatment group was reduced to 4 mg, serum creatinine monitoring was implemented prior to each dose, and the primary efficacy assessment became the comparison of the 4 mg group versus placebo. After these amendments, the rates of deterioration in renal function between the zoledronic acid 4 mg and placebo groups were similar.

At 15 months, fewer men in the zoledronic acid treatment group had SREs than men in the placebo group (33.2% versus 44.2%; P=0.021). Zoledronic acid also increased the median time to first SRE (488 days versus 321 days; P= 0.009)[46]. Median survival was longer in the zoledronic 4 mg group than in the placebo group (546 versus 464 days, P=0.091). Notably, the study was not designed to evaluate the effect of zoledronic acid on survival and the observed difference in overall survival was not statistically significant. Based on the results of this study, zoledronic acid (4 mg intravenously every 3-4 weeks) was approved to treat men with bone-metastatic prostate cancer and disease progression despite first-line hormonal therapy.

CGP 032 / INT 05

In two similarly-designed, multi-center trials, CGP 032 and INT 05, 350 men with CRPC and symptomatic bone metastases were assigned randomly to either intravenous pamidronate (90 mg) or placebo every 3 weeks for 27 weeks[47]. Primary endpoints were self-reported pain, analgesic use, and SREs (defined as pathologic fracture, radiation or surgery to bone, spinal cord compression, or hypercalcemia). Results from the two studies were pooled. Pain scores, analgesic use, proportion of men with at least one SRE by 27 weeks, and survival did not differ between the groups.

Pamidronate decreased urinary NTx markers of osteoclast activity by approximately 50%. In contrast, zoledronic acid decreases urinary markers of osteoclast activity by 70-80%[34]. Less potent suppression of osteoclast activity by pamidronate may have contributed to its lack of efficacy in CGP 032/INT 05. Inclusion of subjects with more advanced disease and use of less precise study endpoints may have also contributed to the negative results.

NCIC CTG PR.6

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) PR.6 study evaluated the palliative benefit of intravenous clodronate in patients with symptomatic, bone-metastatic CRPC. Two-hundred and nine men were treated with mitoxantrone (12 mg/m^2 intravenously every 3 weeks) and prednisone, and were randomly assigned to receive

either intravenous clodronate (1500 mg every 3 weeks) or placebo[48]. Subjects completed pain index and quality of life questionnaires at each visit and recorded analgesic use in daily diaries. The primary end point was palliative response, defined as a two-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 achieved in 46 (46%) of 104 patients on the clodronate arm and in 41 (39%) of 105 patients on the placebo arm (P=0.54). The median duration of response, symptomatic disease progression-free survival, overall survival, and overall quality of life were similar between the arms. Subgroup analysis suggested a possible benefit in men with more severe pain.

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

Denosumab protocol 20050103

In Amgen Inc., protocol 20050103 (NCT 00321620), a randomized, double-blind multicenter study, 1,901 men with CRPC and bone metastases were assigned to denosumab (120 mg subcutaneously every 4 weeks) or zoledronic acid (4 mg intravenously every 4 weeks). The primary endpoint was time to first on-study SRE (pathological fracture, radiation to bone, surgery to bone, or spinal cord compression). The primary objective was to demonstrate non-inferiority of denosumab compared with zoledronic acid. Secondary objectives were to demonstrate superiority of denosumab and comparative safety and tolerability of the two drugs.

In a preliminary report of the study, denosumab was superior to zoledronic acid in delaying the time to first on-study SRE (hazard ratio (HR) 0.82; 95% confidence interval (CI) 0.71-0.95) and reducing rates of multiple SREs (HR=0.82; 95% CI 0.71-0.94) [49,50]. Overall survival and time to disease progression were similar between the groups. Adverse event rates were similar, without a significant difference in osteonecrosis of the jaw (22 in the denosumab arm and 12 in the zoledronic acid arm). Based on these results, denosumab may become the new standard of care for prevention of SREs in men with castration-resistant metastatic prostate cancer.

Castration-sensitive metastatic prostate cancer

MRC PR05 is the only completed, randomized, controlled trial to evaluate the efficacy of a bisphosphonate in metastatic prostate cancer patients receiving first-line hormone therapy (castration). CALGB/CTSU 90202, an ongoing study, is designed to evaluate the efficacy of zoledronic acid in this setting.

MRC PR05

In the Medical Research Council PR05 study, 311 men with prostate and bone metastases who were either initiating or responding to primary ADT were assigned randomly to either oral clodronate (2080 mg daily) or placebo[51]. All men continued primary ADT. The primary study 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 progression-free survival (HR=0.79; 95% CI 0.61-1.02; P=0.066) and overall survival (HR=0.80; 95% CI 0.62-1.03; P=0.082). Men in the clodronate group reported more gastrointestinal problems and required more frequent dose modification of study drug (HR for any adverse event 1.71; 95% CI 1.21-2.41; P=0.002). In exploratory analyses, a short interval between diagnosis of bone

metastases and initiation of investigational treatment was associated with better outcomes. Long-term overall survival data after 258 deaths confirmed 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=0.032) [52]. As the survival benefit of early use of clodronate in castration-sensitive metastatic disease has only recently been reported, the clinical impact of this study is as yet unknown.

CALGB / CTSU 90202

An ongoing randomized controlled trial will help define the role of zoledronic acid in castration-sensitive metastatic prostate cancer. CALGB / CTSU 90202 (NCT00079001) will enroll 680 men with prostate cancer and bone metastases who have initiated ADT within 3 months. Subjects are assigned to zoledronic acid (4 mg intravenously every 4 weeks) or placebo. Subjects will crossover to open-label zoledronic acid at either progression to castration-resistant disease or first SRE. The primary study endpoint is SRE or prostate cancer death. Accrual is ongoing.

Prevention of bone metastasis in nonmetastatic prostate cancer

Two randomized controlled trials to evaluate the efficacy of bisphosphonates for prevention of bone metastases in men with nonmetastatic prostate cancer have been reported. A randomized, placebo-controlled study evaluating denosumab in this setting is underway. Currently, there is no evidence that osteoclast-targeted therapy prevents the subsequent development of symptomatic bone metastasis.

MRC PR04

MRC PR04 evaluated the efficacy of clodronate to prevent symptomatic bone metastases in patients considered to be at high risk of developing bone metastases. The study included 508 men receiving standard treatment for clinical stage T2-T4 prostate cancer with no evidence of bone metastases and WHO performance status 0-2[53]. Men were randomly assigned to either oral clodronate (2080 mg daily) or placebo for 5 years. Most of the subjects received external beam radiation therapy, external beam radiation therapy with hormone therapy, or primary hormone therapy as standard treatment. The primary endpoint was time to development of symptomatic bone metastases or prostate cancer death. At a median follow-up of 10 years, there were 148 events total, with no significant difference between the groups. The overall 5-year survival 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=0.71). In long-term follow-up after 281 deaths (60%), there was no difference in overall survival between the groups (HR 1.12; 95% CI 0.89-1.42, P=0.94). These results are in contrast with the survival benefit seen with clodronate in castration-sensitive metastatic disease (MRC PR05, described above)[52].

Zometa 704

Zometa 704 was designed to evaluate the effects of zoledronic acid on time to first bone metastasis in men with nonmetastatic CRPC. The study included prostate cancer patients with no radiographic evidence of metastases and PSA progression despite ADT. PSA progression was defined as three consecutive rises in serum PSA (measured at least 2 weeks apart), initial PSA rise within 10 months of study entry, and last PSA ≥ 150% of nadir value. Subjects were assigned randomly to zoledronic acid (4 mg intravenously every 4 weeks) or placebo. Bone scans were performed every 4 months. The primary study endpoint was time to first bone metastasis. Target accrual was 991 subjects.

Between September 1999 and September 2002, 398 subjects were enrolled. In December 2001, the Data and Safety Monitoring Board placed the study on hold because the observed event rate was lower than expected. In September 2002 the study was terminated. Time to first bone metastasis was similar for both groups, although the low event rate and early termination of the study preclude evaluation of efficacy.

Analyses of the placebo group from the study have helped characterize the natural history of a rising PSA in men with castrate nonmetastatic prostate cancer[54]. One-third of subjects developed bone metastases at two years. Median bone metastasis-free survival was 30 months. Median time to first bone metastasis and overall survival were not reached. Baseline PSA and PSA velocity independently predicted shorter time to first bone metastasis, metastasis-free survival, and overall survival. Other covariates did not consistently predict clinical outcomes. These observations facilitate the identification of men at high risk for development of bone metastases and informed the design of subsequent clinical trials in this setting.

ZEUS

The Zometa European Study (ZEUS) is an ongoing, open-label, randomized controlled trial evaluating the effect of zoledronic acid on prevention of bone metastasis in patients with high risk prostate cancer[55]. Eligible patients were required to have at least one high risk prognostic factor: PSA ≥ 20 ng/mL, lymph node-positive disease, or Gleason sum of 8-10. As of 2008, 1,433 patients were randomly assigned to standard prostate cancer therapy with or without zoledronic acid (4 mg intravenously every 3 months for 48 months). The primary objective is to demonstrate superiority of zoledronic acid over control in the proportion of patients with at least one bone metastasis after 48 months of treatment. Secondary objectives will evaluate the effects of zoledronic acid on overall survival, symptomatic disease progression, PSA doubling time, and biochemical markers of bone turnover. The study is ongoing.

Denosumab protocol 20050147

Amgen Inc., protocol 20050147 (NCT 00286091) will accrue 1400 men with prostate cancer, no bone metastases, and rising PSA despite current ADT. It will include only subjects at high risk for development of bone metastases based on PSA ≥ 8 ng/dL and/or PSA doubling time ≤ 10 months. Subjects will be 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

The hypogonadal state caused by ADT accelerates loss of BMD with an associated increase in risk of fractures. Several bisphosphonates have been demonstrated to improve BMD in men receiving ADT, including alendronate[56], pamidronate[26,57], zoledronic acid[58,59], and neridronate[60]. Use of selective estrogen receptor modulators (SERMs) such as raloxifene[61] and toremifene[62] constitutes a second strategy to improve BMD in this clinical setting.

To date, there are no FDA-approved medications for fracture prevention in prostate cancer patients. Two positive phase III fracture prevention trials including prostate cancer patients on ADT with a high risk of fracture have recently been reported. The denosumab and toremifene studies are the first trials to demonstrate significant reductions in fracture risk in this patient population. Therefore, these studies are likely to change clinical practice in the near future. Whether such interventions alter the natural history of disease progression is unclear at this time.

Denosumab HALT 138

Denosumab protocol 20040138, or HALT 138, enrolled 1,468 patients receiving ADT who were considered high risk for fracture based on age ≥70, low baseline BMD, or prior history of osteoporotic fracture[63]. Patients were randomly assigned to receive denosumab (60 mg subcutaneously every 6 months) or placebo for three years. The primary endpoint was percent change in BMD in the lumbar spine, with secondary endpoints including change in BMD at other sites and incidence of new vertebral fractures. Compared to placebo, 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%). Further, denosumab therapy reduced the 3-year incidence of new vertebral fractures by 62% (relative risk (RR) 0.38; 95% CI 0.19-0.78; P=0.006). Fractures at any site were reduced in the denosumab group by 28% (P=0.10). Multiple fractures were significantly reduced by 72% (P=0.006). Rates of adverse event were similar in the treatment groups.

Toremifene protocol G300203

Toremifene protocol G300203 (NCT00129142) enrolled 1,389 patients receiving ADT who were considered high risk for fracture due to age ≥70 or low BMD[64]. Subjects were assigned randomly either toremifene (80 mg by mouth daily) or placebo for 2 years. The primary endpoint was incidence of morphometric vertebral fractures. Secondary endpoints included BMD at hip and lumbar spine, breast pain, hot flashes, and lipid profile.

Men treated with toremifene had significantly fewer new vertebral fractures compared with the placebo group (2.5 vs. 4.9%; RR=0.50; P<0.05). Toremifene also significantly increased BMD at the lumbar spine by 2% and at the hip by 1.6%, and decreased breast pain and hot flashes. Lipid profile changes in the toremifene group were favorable (*i.e.*, increased high-density lipoprotein and decreased low-density lipoprotein and triglycerides).

Conclusions

Bone metastases and skeletal complications are major causes of morbidity in men with advanced or metastatic prostate cancer. Taken together, the aforementioned studies support the use of zoledronic acid (4 mg every 3-4 weeks) in one setting: to reduce skeletal complications in men with CRPC and bone metastases. Other less-potent bisphosphonates did not prevent SREs in similar studies. Additional studies are needed to determine the optimal timing, schedule, and duration of bisphosphonate treatment in men with bone metastases.

Recent studies of denosumab in prostate cancer and other diseases (breast cancer, osteoporosis, multiple myeloma) have demonstrated the central role of RANKL signaling in bone metastatic disease. Denosumab was superior to zoledronic acid in treatment of bone-metastatic disease in CRPC, the one setting in which a bisphosphonate is approved for prostate cancer. Furthermore, denosumab has proven efficacy in fracture prevention in men on initial ADT. The SERM toremifene also significantly decreases fracture risk in patients on ADT. Ongoing phase 3 studies will address other important unmet medical needs including metastasis prevention.

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Table 1

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

Study	n	Study Population	Arms	Outcome
Zometa 039 [34,46]	643	Castration-resistant, asymptomatic or minimally symptomatic	4 mg zoledronic acid vs. placebo, every 3 weeks for 15 months	Significant decrease in skeletal related events (SREs) (33.2% vs. 44.2%); trend toward improved survival; established zoledronic acid as standard of care in this setting
CGP 032 / INT 05 [47]	350	Castration-resistant, symptomatic	90 mg pamidronate vs. placebo, every 3 weeks for 27 weeks	No significant difference in pain, analgesic use, or SREs
NCIC CTG Pr.6 [48]	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 [49,50]	1,901	Castration-resistant	120 mg denosumab vs. 4 mg zoledronic acid, every 4 weeks	Primary endpoint: denosumab was non-inferior to zoledronic acid in time to first on-study SRE; secondary endpoint: denosumab was superior to zoledronic acid; no difference in overall survival or adverse event rates
MRC PR05 [51,52]	311	Castration-sensitive	2080 mg daily oral clodronate vs. placebo, for 3 years maximum	Trend toward improved bone progression-free survival (P-0.066); significantly improved 8-year overall survival (22% vs. 14%, HR=0.077; P=0.032)
CALGB / CTSU 90202	680*	Castration-sensitive	4 mg zoledronic acid vs. 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

* targeted accrual

Table 2

Randomized Controlled Trials of Osteoclast-targeted Therapies in Prevention of Bone Metastasis in Non-metastatic Prostate Cancer

Study	n	Study Population	Arms	Outcome
MRC PR04 [53]	508	Clinical stage T2-T4	2080 mg daily oral clodronate vs. placebo, for 5 years	No difference in development of bone metastasis or overall survival
ZEUS[55]	1,433	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* Pimary objective: evaluate superiority of zoledronic acid over control in incidence of bone metastasis
Denosumab protocol 20050147	1,400*	Castration-resistant, high-risk by PSA criteria	120 mg denosumab vs. placebo, every 4 weeks	*Ongoing* Primary endpoint: bone metastasis-free survival Final results expected, 2010.

* targeted accrual

Table 3

Randomized Controlled Trials of Fracture Prevention in Prostate Cancer

Study	n	Study Population	Arms	Outcome
Denosumab HALT 138 [63]	1,468	Current androgen-deprivation therapy; no metastases; high risk for fracture	60 mg denosumab vs. 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 [64]	1,389	Current androgen-deprivation therapy; high risk for fracture	80 mg daily oral toremifene vs. placebo	Fewer new vertebral fractures (2.5% vs. 4.9%, $P<0.05$); increased bone mineral density, decreased breast pain, decreased hot flashes, favorable lipid profile changes