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Osteoclast targeted therapy for prostate cancer: Bisphosphonates and beyond☆

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Abstract

Bone metastases are a major cause of morbidity for men with prostate cancer. Although typical bone metastases from prostate cancer appear osteoblastic by radiographic imaging, excess number and activity of both osteoblasts and osteoclasts characterize most “osteoblastic” bone metastases. Additionally, pathological osteoclast activation is associated with increased risk of skeletal complications, disease progression, and death. Zoledronic acid, a potent intravenous bisphosphonate, reduces markers of osteoclast activity and significantly decreases the risk of skeletal complications in men with androgen-independent prostate cancer and bone metastases. Additional studies are needed to determine the optimal timing, schedule, and duration of bisphosphonate treatment in men with bone metastases as well as the potential role of bisphosphonates in other settings, including the prevention of bone metastases. Denosumab is a human monoclonal antibody that binds and neutralizes human receptor activator of NF-κB ligand (RANKL), a critical mediator of osteoclast activation, differentiation, and survival. Three ongoing pivotal studies involving more than 4,500 subjects will evaluate the role of denosumab for prevention of treatment-related fractures, bone metastases, and disease-related skeletal complications in men with prostate cancer.

Keywords

Prostate cancer; Bone metastases; Osteoclast; Bisphosphonate; Denosumab

Introduction

Bone is constantly shaped and repaired by a process termed remodeling. Bone remodeling is the major metabolic activity regulating bone structure and function in adulthood. This process involves the breakdown and formation of bone by the coordinated action of osteoclasts and osteoblasts. Remodeling takes place in discrete microscopic units throughout the skeleton. The remodeling process requires migration of osteoclasts to these sites, resorption of bone, apoptosis of osteoclasts, and subsequent new bone formation by osteoblasts.

Osteoclasts are tissue-specific macrophages derived from hematopoietic stem cells of the monocyte/macrophage lineage. Bone resorption is a multistep process initiated by proliferation of immature osteoclast precursors, commitment of these cells to the osteoclast phenotype, and lastly degradation of the bone matrix by mature multinucleated osteoclasts. The bone matrix is a storehouse of growth factors. Bone resorption releases a variety of factors that activate osteoblasts, including transforming growth factor-β, basic fibroblast

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growth factor, platelet-derived growth factor, and insulin-like growth factors. Osteoblasts are derived from stromal stem cells. Osteoblasts synthesize and secrete the organic matrix.

Pathophysiology of osteoblastic metastases

Most bone metastases from prostate cancer appear osteoblastic by radiographic imaging. Osteolytic and osteoblastic lesions represent two ends of a continuum, however, and morphometric studies suggest that excess activity of both osteoblasts and osteoclasts characterize most bone metastases. Osteoblastic metastases from prostate cancer have increased osteoblast number and activity, increased bone volume, and increased bone mineralization rate [1]. Osteoclast number and activity are also increased in osteoblastic metastases, bone adjacent to metastases, and distant uninvolved bone [1,2]. Biochemical markers of osteoclast activity are elevated in men with osteoblastic metastases from prostate cancer [3,4]. Pathological acceleration of bone remodeling results in disorganized bone with impaired biomechanical properties. Elevated markers of osteoclast activity predict the risk for subsequent skeletal complications [5], suggesting that cancer-mediated osteoclast activation contributes to the clinical complications of metastatic disease.

Clinical manifestations of bone metastases

Pain is the most frequent symptom of metastatic prostate cancer. Metastases involving the vertebrae may cause spinal cord compression, nerve root compression, or cauda equina syndrome. Metastases to the base of the skull can impinge on cranial nerves. Clinical fractures are common with most fractures involving the vertebral bodies. Pathological fractures of long bones are unusual. Hypocalcemia due to excess deposition of calcium in newly formed bone is common but rarely associated with symptoms. Most men with metastatic prostate cancer have normochromic, normocytic anemia.

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate distinguished by a phosphorus-carbon-phosphorus backbone that renders them resistant to hydrolysis. The R1 and R2 carbon side chains determine the pharmacological properties of bisphosphonates [6]. Most bisphosphonates contain a hydroxyl group at the R1 position that confers high affinity binding to calcium phosphate. The R2 side chain is the essential determinant of antiresorptive potency. Zoledronic acid is the most potent tested bisphosphonate. In preclinical models of bone resorption, for example, zoledronic acid is at least 100 times more potent than either clodronate or pamidronate and at least 1,000 times more potent than etidronate.

Bisphosphonates inhibit normal and pathological osteoclast-mediated bone resorption by several mechanisms. Bisphosphonates directly inhibit osteoclast activity by cellular mechanisms that affect osteoclast attachment, differentiation, and survival. They also reduce osteoclast activity indirectly through effects on osteoblasts.

Bisphosphonates are an established part of supportive care for patients with bone metastases. In 1995, intravenous pamidronate (Aredia®) 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. In 2002, intravenous zoledronic acid (Zometa®) 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 3,000 patients [7–9].

Bisphosphonates for androgen-independent metastatic prostate cancer

Three contemporary randomized controlled trials have evaluated the efficacy of bisphosphonates for men with androgen-independent prostate cancer and bone metastases (Table 1).

In the Zometa 039 study, 643 men with androgen-independent prostate cancer and asymptomatic or minimally symptomatic bone metastases were assigned randomly to intravenous zoledronic acid (4 or 8 mg every 3 weeks) or placebo [9]. All men continued androgen deprivation therapy (bilateral orchiectomies or treatment with a gonadotropin-releasing hormone agonist) throughout the study and received additional antineoplastic therapy at the discretion of the investigator. The primary study endpoint was the proportion of men who experienced one or more skeletal related event (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 prompted two study amendments. In the first amendment, the infusion time for zoledronic acid was increased from 5 to 15 minutes. In the second amendment, the zoledronic 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 vs. 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 4 mg had skeletal related events than men in the placebo group (33% vs. 44%; $P = 0.02$). Zoledronic acid also increased the median time to first skeletal related event (488 days vs. 321 days; $P = 0.01$) [10]. Median survival was longer in the zoledronic 4 mg group than in the placebo group (546 vs. 464 days, $P = 0.09$). 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 to 4 weeks) was approved to treat men with prostate cancer metastatic to bone and disease progression despite first line hormonal therapy.

In two multicentered trials, protocol 032 and INT 05, 350 men with androgen-independent prostate cancer and symptomatic bone metastases were assigned randomly to either intravenous pamidronate (90 mg every 3 weeks) or placebo every 3 weeks for 27 weeks [11]. Efficacy was measured via self-reported pain score, analgesic use, the proportion of patients with a skeletal-related event (SRE; defined as pathologic fracture, radiation or surgery to bone, spinal cord compression, or hypercalcemia).

Primary endpoints were self-reported pain, analgesic use, and skeletal-related events. Results from the two studies were pooled. Pain scores, analgesic use, proportion of men with at least one skeletal related event by 27 weeks, and survival did not differ between the groups.

Pamidronate decreased urinary markers of osteoclast activity by approximately 50%. In contrast, zoledronic acid decreased urinary markers of osteoclast activity by 70% to 80% [9]. Less potent suppression of osteoclast activity by pamidronate may explain, at least in part, the lack of efficacy in protocol 032/INT05. Inclusion of subjects with more advanced disease and use of less precise study endpoints may also have contributed to the apparent lack of efficacy with pamidronate.

National Cancer Institute of Canada Pr06 (NCIC Pr06) study evaluated the palliative benefit of intravenous clodronate in men with symptomatic metastatic prostate cancer. Two hundred nine men with androgen-independent prostate cancer and symptomatic bone metastases were assigned randomly to either mitoxantrone, prednisone, and intravenous clodronate (1,500 mg every 3 weeks) vs. mitoxantrone, prednisone, and placebo [12]. Subjects completed pain index and quality of life questionnaires at 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 (44%) 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 possible benefit in men with more severe pain.

Taken together, these results show that zoledronic acid, but not other bisphosphonates, decreases the risk of skeletal complications in men with androgen-independent prostate cancer and bone metastases.

Bisphosphonates for androgen-sensitive metastatic prostate cancer

Medical Research Council (MRC) Pr05 is the only completed randomized controlled trial to evaluate the efficacy of bisphosphonates in men with androgen-sensitive metastatic prostate cancer. Cancer and Leukemia Group B/Cancer Trials Support Unit (CALGB/CTSU) 90202 was recently initiated to evaluate the efficacy of zoledronic acid in this setting.

In the Medical Research Council Pr05 study, 311 men with prostate and bone metastases who were either initiating or responding to primary androgen deprivation therapy were assigned randomly to either oral clodronate (2,080 mg/day) or placebo [13]. All men continued primary androgen deprivation therapy. The primary study endpoint was symptomatic skeletal disease progression or prostate cancer death. After a median follow-up of 59 months, the clodronate group had nonsignificant improvements in progression-free survival (hazard ratio 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 (hazard ratio 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.

An ongoing randomized controlled trial will help define the role of zoledronic acid in hormone sensitive metastatic prostate cancer. CALGB/CTSU 90202 will enroll 680 men with prostate cancer and bone metastases who have initiated androgen deprivation therapy within 3 months. Subjects will be assigned to zoledronic acid (4 mg intravenously every 4 weeks) or placebo. Subjects will cross over to open-label zoledronic acid at either progression to hormone refractory disease or first skeletal related event. The primary study endpoint is skeletal related event or prostate cancer death.

In summary, there is no compelling clinical evidence supporting bisphosphonates therapy for androgen-sensitive metastatic prostate cancer. CALGB/CTSU 90202 will provide important information about long-term safety and optimal timing of bisphosphonate therapy in men with bone metastases.

Bisphosphonates for prevention of bone metastases

Two randomized controlled trials to evaluate the efficacy of bisphosphonates for prevention of bone metastases in men with nonmetastatic prostate cancer have been reported.

MRC Pr04 evaluated the efficacy of clodronate to prevent symptomatic 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 [14]. Men were randomly assigned to either oral clodronate (2,080 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 7 years, there were 131 events total. There was no significant difference between the groups although a trend to better outcome in favor of the placebo group was observed (hazard ratio 1.29, 95% CI 0.92–1.82; $P = 0.13$). The overall 5-year survival was 78% for the entire study population. Overall survival was similar in both groups (hazard ratio 1.03, 95% CI 0.76–1.39; $P = 0.86$).

Zometa 704 was designed to evaluate the effects of zoledronic acid on time to first bone metastasis in men with progressive castrate nonmetastatic prostate cancer. The study included men with prostate cancer, no radiographic evidence of metastases, and PSA progression despite androgen deprivation therapy. PSA progression was defined as 3 consecutive rises in serum PSA (measured at least 2 weeks apart), initial PSA rise within 10 months of study entry, and last PSA ≥ 150% 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 prior to reaching target accrual of 991 subjects 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 [15]. One-third of subjects had developed bone metastases at 2 years. Median bone metastasis-free survival was 30 months. Median time to first bone metastases and overall survival were not reached. Baseline PSA and PSA velocity independently predicted shorter time to first bone metastasis. Baseline PSA and PSA velocity also independently predicted overall survival and metastasis-free survival. Other covariates did not consistently predict clinical outcomes. These observations may facilitate the identification of men at high risk for development of bone metastases and inform the design of future clinical trials in this setting.

Bisphosphonates—practical considerations

Available evidence supports treatment with zoledronic acid (4 mg every 3 to 4 weeks) to reduce the risk of skeletal complications in men with androgen-independent prostate cancer and bone metastases. There are limited data about the optimal duration of therapy. Based on clinical practice guidelines for breast cancer and multiple myeloma [16,17], however, zoledronic acid treatment should continue until treatment-related adverse events or substantial decline in performance status. Other bisphosphonates (including pamidronate

and clodronate) do not prevent disease-related skeletal complications in men with metastatic prostate cancer.

Reduction in risk of skeletal complications in men with bone metastases should be weighed against potential adverse effects of zoledronic acid. The most common treatment-related adverse event is an acute phase reaction, a transient flu-like syndrome of fever, arthralgias, and myalgias starting within 24 hours after treatment [18]. Hypocalcemia is also common but rarely associated with symptoms. Supplemental calcium (500–1,000 mg daily) and vitamin D (400 IU daily) should be prescribed to reduce the risk of symptomatic hypocalcemia. Parenteral vitamin D should be considered for patients with known vitamin D deficiency or for unusual cases of refractory hypocalcemia. Renal toxicity is a recognized and potentially serious adverse effect of zoledronic acid [19] New renal safety guidelines recommend dose reductions for patients with baseline estimated creatinine clearance between 30 and 60 ml/minute and no treatment for patients with creatinine clearance less than 30 ml/minute [20]. Renal function monitoring is recommended before each treatment. Zoledronic acid and other bisphosphonates are also associated with increased risk of osteonecrosis of the jaw (ONJ) [21,22]. Most patients who develop ONJ have pre-existing dental problems. Good oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during bisphosphonate therapy are recommended to reduce risk of ONJ.

The role of bisphosphonates for prevention of disease-related skeletal complications in other clinical settings is unknown. CALGB/CTSU 90202 will define the role of zoledronic acid in androgen-dependent (hormone sensitive) metastatic prostate cancer and provide important information about the best timing and long-term safety of bisphosphonate therapy. There is no evidence that bisphosphonates prevent bone metastases in men with prostate cancer. The role of bisphosphonates to treat and prevent osteoporosis during androgen deprivation therapy for prostate cancer is reviewed elsewhere [23].

Denosumab—RANKL inhibition for prostate cancer

The RANK signaling pathway regulates the activation, differentiation, proliferation, and apoptosis of osteoclasts [24]. The pathway consists of receptor activator of NF-κB ligand (RANKL), its receptor RANK, and its decoy receptor osteoprotegerin (OPG). RANKL binds and activates RANK, a transmembrane receptor expressed on hematopoietic stem cells and osteoclasts. RANK expression on stem cells is required for osteoclast differentiation and activation. Hormones and other factors that stimulate bone resorption induce the expression of RANKL by bone stromal cells and osteoblasts.

Denosumab is a human monoclonal antibody that binds and neutralizes human RANKL. In postmenopausal women, a single administration of denosumab resulted in marked (>80%) and sustained (6 month) suppression of osteoclast activity [25]. Denosumab is in development for the treatment and prevention of postmenopausal osteoporosis, treatment-related osteoporosis in men with prostate cancer and women with breast cancer, and for the treatment and prevention of bone metastases. Denosumab achieves rapid and sustained inhibition of osteoclast activity in postmenopausal women and patients with multiple myeloma or bone metastases from breast cancer [26,27]. In contrast to bisphosphonates, denosumab does not accumulate in bone and achieves sustained osteoclast inhibition due at least in part to a long circulatory half-life (>30 days).

Three ongoing pivotal studies involving more than 4,500 subjects will evaluate the efficacy of denosumab in men with prostate cancer (Table 2).

Amgen protocol 138 has accrued 1,468 men with prostate cancer receiving current androgen deprivation therapy, and at increased risk for fracture based on older age and/or low bone mineral density. Subjects are assigned to denosumab or placebo. Study endpoints are incident fractures and change in bone mineral density.

Amgen protocol 147 will accrue 1,400 men with prostate cancer, no bone metastases, and rising PSA despite current androgen deprivation therapy. Only subjects at high risk for development of bone metastases based on PSA ≥ 8 ng/dl and/or PSA doubling time ≤ 10 months are included. Subjects are assigned to denosumab or placebo. The primary study endpoint is bone metastasis-free survival.

Amgen protocol 103 will accrue 1,700 men with prostate cancer, bone metastases, and disease progression despite current androgen deprivation therapy. Subjects are assigned to denosumab or zoledronic acid, the current standard therapy for prevention of skeletal complications in this setting. The primary endpoint is time to first on study skeletal related event (pathological fracture, radiation to bone, surgery to bone, or spinal cord compression). The study is designed to demonstrate that denosumab is not inferior to zoledronic acid.

The denosumab program in prostate cancer has the potential to expand the role of bone-targeted therapy into prevention of treatment-related fractures and prevention of bone metastases in men. In addition, denosumab may improve the therapeutic index for prevention of skeletal complications in men with bone metastases. Denosumab does not have the potential for renal toxicity associated with bisphosphonates. The distinct mechanism of action and pharmacokinetics of denosumab also raise the possibility that it will not be associated with ONJ.

Conclusions

Skeletal complications are a major cause of morbidity for men with metastatic prostate cancer. Zoledronic acid decreases the risk of disease-related skeletal complications in men with androgen-independent prostate cancer and bone metastases. Further studies are necessary to determine the best timing, schedule, and duration of bisphosphonate therapy for men with bone metastases. Additional studies are also warranted to determine the role of bisphosphonates in other settings, including the prevention of bone metastases in men with high-risk disease. Three ongoing pivotal studies involving more than 4,500 men with prostate cancer will evaluate the role of denosumab, a RANKL targeted therapy, for prevention of treatment-related fractures, bone metastases, and disease-related skeletal complications.

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Table 1

Contemporary randomized controlled trials of bisphosphonates for metastatic prostate cancer

Study	*n*	Study population	Arms	Outcome
Zometa 039 [9,10]	643	Asymptomatic, androgen-independent	Zoledronic acid vs. placebo	Significant decrease in skeletal related events
Study 032/INT [11]	350	Symptomatic, androgen-independent	Pamidronate vs. placebo	No significant difference in pain, analgesic use, or skeletal related events
NCIC Pr06 [12]	204	Symptomatic, androgen-independent	Mitoxantrone and prednisone ± clodronate	No significant difference in palliative response
MRC Pr05 [13]	311	Androgen-dependent	Clodronate vs. placebo	Trend toward improved bone progression-free survival

Table 2
Ongoing randomized controlled trials of denosumab for prostate cancer

Study/purpose	*n*	Study population	Arms	Endpoint(s)
Amgen protocol 138/ fracture prevention	1,468	Current androgen deprivation therapy; no metastases	Denosumab vs. placebo	Incident vertebral fractures bone mineral density
Amgen protocol 147/ metastasis prevention	1,400	Androgen-independent; no bone metastases	Denosumab vs. placebo	Bone metastasis-free survival
Amgen protocol 103/ prevention of skeletal complications	1,700	Androgen-independent; bone metastases	Denosumab vs. zoledronic acid	Skeletal-related events