Osteoclast-targeted therapy for metastatic prostate cancer

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Bone metastases and skeletal complications are major causes of morbidity in men with prostate cancer. Despite the osteoblastic appearance of bone metastases on imaging studies, patients with bone metastases have elevated markers of bone resorption, indicative of high osteoclast activity. Indeed, increased osteoclast activity is independently associated with higher risk of subsequent skeletal complications. Therapies aimed at reducing osteoclast activity would theoretically diminish disease-related skeletal complications, bone metastases and treatment-related fractures. Phase III clinical trials to address the role of osteoclast-targeted therapy in metastatic prostate cancer are reviewed here. Zoledronic acid, a potent bisphosphonate, significantly decreased the risk of skeletal complications in men with androgen-independent prostate cancer and bone metastases. Ongoing studies will evaluate the use of bisphosphonates or denosumab, a monoclonal antibody that inhibits the receptor activator of nuclear factor-κB ligand signaling in the prevention of bone metastases or skeletal complications. Additional studies are needed to determine the optimal timing, schedule and duration of bisphosphonate treatment in men with bone metastases. The results of these trials in the near future may herald further evolution in the targeting of osteoclasts and optimal supportive care in men with prostate cancer.

Keywords: bisphosphonate, denosumab, metastasis, osteoclast, prostate cancer, receptor activator of nuclear factor-kB ligand, zoledronic acid

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The American Cancer Society estimates, for 2007, that there will be over 218,000 new cases of prostate cancer in the USA, accounting for 29% of cancer diagnoses in men in the USA 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 androgen-independent metastatic prostate cancer undergoing therapy [2,3] and 90% of patients at autopsy [4]. The most common sites of metastasis within the skeleton are the vertebral column, pelvis, ribs, long bones and skull, which are the areas of active hematopoiesis in adults and, as such, 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. Vertebral metastases may cause compression fractures, spinal cord compression, nerve root compression and cauda equina syndrome. Pathologic fractures of proximal long bones can occur, albeit at lower rates [5]. Hypocalcemia, as a result of excessive bone formation, and subsequent secondary hyperparathyroidism are common [6]. Anemia is commonly seen, with a multifactorial etiology including ineffective erythropoiesis due to bone metastasis and cancer therapies.

Pathophysiology

Numerous factors may account for the preference of cancers to metastasize to bone, including high blood flow to bone marrow, a rich growth factor milieu in areas of active hematopoiesis, as well as a large repository of immobilized growth factors in the matrix [7]. Bone metastases in prostate cancer patients are predominantly osteoblastic. However, markers of bone resorption are higher in patients with bone metastasis compared with those without, indicative of elevated bone turnover despite the osteoblastic radiographic appearance [8,9]. Osteoclast number and activity are increased in osteoblastic metastases and in adjacent bone [10,11]. Indeed, increased markers of osteoclast activity and bone resorption were independently associated with risk of subsequent skeletal complications, suggesting that cancer-mediated osteoclast activation contributes to the clinical complications of metastatic disease [5].

Osteoclasts, which arise from the monocyte lineage in the bone, are activated by local and systemic factors to resorb bone during normal bone remodeling and in pathologic states. Osteoclasts express receptor activator of nuclear factor-κB (RANK), a member of the tumor necrosis factor (TNF) receptor superfamily, which is activated by RANK ligand (RANKL).

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RANK expression is required for osteoclast differentiation and activation. RANKL is expressed by bone marrow stromal cells (also known as 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 protects bone from resorption [12]. 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 [13], whereas targeted deletion of OPG causes osteopenia [14]. Bone resorption by activated osteoclasts occurs by the release of proteases that dissolve the matrix, releasing the immobilized growth factors, further enriching the marrow's growth factor milieu [7,15].

Parathyroid hormone (PTH) stimulates osteoclast formation by inducing RANKL expression in bone marrow stromal cells and osteoblasts [7]. Hypocalcemia caused by osteoblastic calcium-phosphate deposition may stimulate PTH production, with resultant secondary hyperparathyroidism. Thus, 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 may contribute to disease progression.

Therapy for prostate cancer also influences osteoclast activity. Patients receiving androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) agonists exhibit increased PTH-mediated osteoclast activation, as well as biochemical markers of osteoblast and osteoclast activity [16,17]. It has been demonstrated in preclinical models that androgen and estrogen withdrawal (which are seen in men treated with GnRH agonists) can both augment the induction by PTH of the bone-resorbing cytokine IL-6, which may account for the increased skeletal sensitivity to PTH in these patients [17]. Osteoporosis is another important consequence of androgen-deprivation therapy and may lead to fractures and significant morbidity.

Modulating the activity of osteoclasts 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 [18]. Therefore, an unanswered question in bone metastasis biology is whether bone resorption precedes osteoblastic metastatic development or is a consequence of increased bone formation.

Given the osteoblastic nature of bone metastases from prostate cancer, osteoblast activity is another rational target for therapeutic inhibition. 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 [19].

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. Most of these agents have been explored as treatments for osteoporosis, and their uses in treatment of prostate cancer are in varying stages of development. Other potential targets of osteoclast signaling in prostate cancer (e.g., Src tyrosine kinases, integrins and matrix metalloproteinases) that are in preclinical or very early-stage clinical development will not be reviewed here.

Bisphosphonates

Bisphosphonates are synthetic analogs of pyrophosphate, a normal component of bone matrix. They are rapidly cleared from the circulation and bind to areas of exposed bone mineral. Bisphosphonates inhibit osteoclast activity via several mechanisms. By binding hydroxyapatite crystals, bisphosphonates diminish their availability for osteoclast-mediated resorption. Bisphosphonates have also been demonstrated to directly inhibit the activities of osteoclasts and their precursors, including recruitment, differentiation, attachment and survival [20]. Bisphosphonates have been shown *in vitro* to indirectly inhibit osteoclast differentiation and activation via effects on osteoblasts [20]. Bisphosphonates have been demonstrated *in vitro* to induce apoptosis and inhibit RANKL expression in prostate cancer cells, which may further diminish osteoclast activity [21].

The potency of bisphosphonates is determined by the R2 side chain. Those that contain a primary amino group at R2 (e.g., pamidronate) are up to 100-fold more potent than non-amino 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 [22,23]. 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 [24–26].

The ability of bisphosphonates to delay the appearance and progression of visceral and skeletal metastasis is unclear. Diel *et al.* randomized 302 women with primary breast cancer considered to be at high risk of bone metastasis (due to the presence of tumor cells in the bone marrow) to receive oral adjuvant clodronate or standard follow-up for 2 years [27]. Patients who received clodronate had a significantly lower incidence of osseous and visceral metastases and fewer bony metastases. However, subsequent studies that randomized breast cancer patients to adjuvant oral clodronate versus placebo for 2 or 3 years did not exhibit a significant reduction in the occurrence of bone metastasis [28,29], although the inclusion criteria of these studies were slightly different. Preclinical data of zoledronic acid in mouse models of metastatic breast cancer indicate a significant reduction in bone and visceral metastases with zoledronic acid treatment [30]. The role of bisphosphonates, especially the more potent aminobisphosphonates, in prevention of metastasis in prostate cancer patients remains undefined.

Bisphosphonates are also important for the prevention of bone loss and consequent skeletal complications due to androgen deprivation therapy in prostate cancer patients without bone metastases. In randomized studies in men without bone metastases receiving a GnRH agonist, pamidronate was shown to prevent loss of bone mineral density (BMD) [31], and zoledronic acid was shown to increase BMD, as well as suppress markers of osteoclast activity [32]. These studies were designed to examine bisphosphonates and bone loss, but were not powered to examine whether treatment impacted fracture risk or appearance of bone metastasis.

Denosumab

Denosumab (AMG 162, Amgen Inc., CA, USA) is a fully human monoclonal IgG_2 antibody directed against RANKL, with an extremely high affinity for human RANKL (Kd ~10^{-12} M) [33]. In contrast to bisphosphonates, denosumab does not accumulate in the bone and has a long circulatory half-life (>30 days). Denosumab has been examined in postmenopausal 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 h), marked (>80%) and sustained (6 month) suppression of osteoclast activity [34]. In patients with multiple myeloma or bone metastasis from breast cancer, denosumab was well tolerated and achieved rapid and sustained suppression of osteoclast activity [35,36].

Osteoprotegerin

RANKL inhibition has also been tested using recombinant osteoprotegerin. The Fc portion of the immunoglobulin heavy chain was fused to the amino terminus of OPG, to generate recombinant Fc-OPG. Amgen Inc. performed a dose-escalation clinical trial examining inhibition of RANKL by Fc-OPG in postmenopausal women with osteoporosis [37]. The highest dose of OPG decreased markers of osteoclast activity by 80% after 4 days, with significant effects lasting 45 days; markers of osteoblast activity were not changed. No serious adverse effects were reported. A different formulation of OPG, AMGN-0007, was examined in patients with multiple myeloma or breast cancer with radiographically confirmed lytic bone lesions [38]. AMGN-0007 was well tolerated and exhibited comparable effects on bone metabolism to pamidronate.

In comparison of the two forms of RANKL inhibition, denosumab was noted to be more potent than recombinant OPG, with greater decreases in bone turnover markers and longer duration of action [37]. Furthermore, two theoretical risks inherent to recombinant OPG are not applicable to denosumab:

- The generation of anti-Fc-OPG antibodies, which may cross-react and interfere with endogenous OPG function;
- The binding of OPG to TNF-related apoptosis-inducing ligand (TRAIL), which may interfere with its role in the normal defense mechanism against tumorigenesis [37].

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 the inhibition of bone remodeling by targeting of osteoclast activity influence disease progression? Three common clinical scenarios have been the subjects of previous or current study. Does inhibition of bone remodeling reduce skeletal-related events (SREs; including pathologic fracture, need for radiation therapy to bone, need for surgery to bone and spinal cord compression) in prostate cancer patients with bone metastases and androgen-independent disease? Are SREs reduced in patients with bone metastases and androgen-sensitive disease? Does osteoclast-targeted therapy prolong bone metastasis-free survival in men with androgen-independent disease and no bone metastases at baseline? The clinical trials addressing these questions are presented below and are summarized in **Tables 1 & 2**.

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. One ongoing study compares denosumab with zoledronic acid in this setting.

Zometa 039

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 [26]. All men continued androgen-deprivation therapy (bilateral orchiectomies or treatment with a GnRH agonist) throughout the study and received additional antineoplastic therapy at the discretion of the investigator. The primary study end point 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 prompted two study amendments. In the first amendment, the infusion time for zoledronic acid was increased from 5 to 15 min, with an increase in infusate volume from 50 to 100 ml. 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 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 4-mg group had skeletal-related events than men in the placebo group (33.2 vs 44.2%; $p = 0.021$). Zoledronic acid also increased the median time to first SRE (488 vs 321 days; $p = 0.009$) [39]. Median survival was longer in the zoledronic 4-mg group than in the placebo group (546 vs 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.

Associated biochemical studies indicated a significant reduction in osteoclast activity (as measured by urine markers of bone resorption, *N*-telopeptide-, pyridinoline- and deoxypyridinoline-to-creatinine ratios) in patients who received zoledronic acid. A serum marker of osteoblast activity (bone alkaline phosphatase) was significantly higher in patients who received placebo. Together, these studies suggest that osteoblastic activity may be linked to osteoclastic activity, in contrast to the aforementioned animal study in which zoledronic acid inhibited osteoclastic activity but did not inhibit the development of osteoblastic lesions [18].

Based on the results of this study, zoledronic acid (4 mg intravenously every 3–4 weeks) was approved to treat men with prostate cancer metastatic to bone and disease progression despite first-line hormonal therapy.

CGP 032/INT 05

In two multicentered trials, CGP 032 and INT 05, 350 men with androgen-independent prostate cancer and symptomatic bone metastases were assigned randomly to either intravenous pamidronate (90 mg) or placebo every 3 weeks for 27 weeks [40]. Primary end points 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 skeletal-related event by 27 weeks and survival did not differ between the groups.

Table 1. Contemporary randomized controlled trials of bisphosphonates for metastatic prostate cancer.

Study	n	Study population	Arms	Outcome	Ref.
Zometa 039	643	Asymptomatic, androgen-independent	Zoledronic acid versus placebo	Significant decrease in skeletal related events	[26,39]
CGP 032/INT 05	350	Symptomatic, androgen-independent	Pamidronate versus placebo	No significant difference in pain, analgesic use or skeletal related events	[40]
NCIC CTG Pr.6	204	Symptomatic, androgen-independent	Mitoxantrone and prednisone ± clodronate	No significant difference in palliative response	[41]
MRC PR05	311	Androgen-dependent	Clodronate versus placebo	Trend toward improved bone progression-free survival and overall survival	[42]
CALGB/CTSU 90202	680*	Androgen-dependent	Zoledronic acid versus placebo	Ongoing	
MRC PR04	508	Nonmetastatic, high-risk	Clodronate versus placebo	No difference in development of bone metastasis or overall survival	[43]

Targeted accrual.

Pamidronate decreased urinary markers of osteoclast activity by approximately 50%. By contrast, zoledronic acid decreased urinary markers of osteoclast activity by 70–80% [26]. Less potent suppression of osteoclast activity by pamidronate may explain, at least in part, the lack of efficacy in CGP 032/INT 05. Inclusion of subjects with more advanced disease and use of less precise study end points may also have contributed to the apparent lack of efficacy with pamidronate.

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 men with symptomatic metastatic prostate cancer. A total of 209 men with androgen-independent prostate cancer and symptomatic bone metastases were assigned randomly to mitoxantrone, prednisone and intravenous clodronate (1500 mg every 3 weeks) versus mitoxantrone, prednisone and placebo [41]. 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 out of 104 patients (44%) on the clodronate arm and in 41 out of 105 patients (39%) 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.

Table 2. Ongoing randomized controlled trials of denosumab for prostate cancer.

Study/purpose	n	Study population	Arms	End point(s)
Amgen Protocol 138/fracture prevention	1468	Current androgen deprivation therapy; no metastases	Denosumab versus placebo	Incident vertebral fractures, bone mineral density
Amgen Protocol 20050147/metastasis prevention	1400*	Androgen-independent, no bone metastases	Denosumab versus placebo	Bone metastasis-free survival
Amgen Protocol 20050103/prevention of skeletal complications	1700*	Androgen-independent, bone metastases	Denosumab versus zoledronic acid (noninferior)	Skeletal-related events

Targeted accrual.

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 androgen-independent prostate cancer and bone metastases.

Amgen protocol 20050103

Amgen Inc. protocol 20050103 (NCT 00321620) is a randomized, double-blind, multicenter study in which men with androgen-independent prostate cancer and bone metastases are assigned to denosumab or zoledronic acid. The primary end point is time to first on-study SRE (pathological fracture, radiation to bone, surgery to bone or spinal cord compression). The study will accrue 1700 men and is designed to demonstrate that denosumab is not inferior to zoledronic acid. This study is currently ongoing.

Androgen-sensitive metastatic prostate cancer

MRC PR05 is the only completed, randomized controlled trial to evaluate the efficacy of a bisphosphonate in men with androgen-sensitive metastatic prostate cancer. CALGB/CTSU 90202, an ongoing study, is designed to evaluate the efficacy of zoledronic acid in this setting.

MRC PR05

In the MRC PR05 study, 311 men with prostate cancer and bone metastases that were either initiating or responding to primary androgen-deprivation therapy were assigned randomly to either oral clodronate (2080 mg daily) or placebo [42]. All men continued primary androgen-deprivation therapy. The primary study end point was symptomatic skeletal disease progression or prostate cancer death. After a median follow-up of 59 months, the clodronate group had nonsignificant improvements in bone progression-free survival (hazard ratio [HR]: 0.79; 95% confidence interval [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.

CALGB/CTSU 90202

An ongoing randomized controlled trial will help to define the role of zoledronic acid in androgen-sensitive metastatic prostate cancer. CALGB/CTSU 90202 (NCT00079001) 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 crossover to open-label zoledronic acid at either progression to androgen-independent disease or first skeletal-related event. The primary study end point is SRE or prostate cancer death.

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

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.

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 of 0–2 [43]. 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 end point was time to development of symptomatic bone metastases or death from prostate cancer. At a median follow-up of 10 years, there were a total of 148 events, with no significant difference between the groups. The overall 5-year survival was 78% for the entire study population. Prostate cancer death rates were similar in both groups (HR: 1.07; 95% CI: 0.76–1.49; p = 0.71).

Zometa 704

Zometa 704 was designed to evaluate the effects of zoledronic acid on time to first bone metastasis in men with progressive castrate non-metastatic 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 three consecutive rises in serum PSA (measured at least 2 weeks apart), initial PSA rise within 10 months of study entry and last PSA greater than 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 end point 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 to characterize the natural history of a rising PSA in men with castrate non-metastatic prostate cancer [44]. A 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, metastasis-free survival and overall survival, whereas other covariates did not consistently predict clinical outcomes. These observations may facilitate the identification of men at high risk of development of bone metastases and inform the design of future clinical trials in this setting.

In summary, there is no evidence that 5 years of oral clodronate prevents the subsequent development of symptomatic bone metastasis. Trials of other bisphosphonates in this setting have not been reported.

Amgen protocol 20050147

Amgen protocol 20050147 (NCT 00286091) will accrue 1400 men with prostate cancer, no bone metastases and rising PSA despite current androgen-deprivation therapy. Only subjects at high risk of development of bone metastases based on a PSA of 8 ng/dl or more and/or PSA doubling time of less than 10 months will be included. Patients will be randomly assigned to denosumab or placebo. The primary end point is bone metastasis-free survival. This study is currently ongoing.

Conclusion

Bone metastases and skeletal complications are major causes of morbidity in men with 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 androgen-independent prostate cancer and bone metastases. Other less potent bisphosphonates (including pamidronate and clodronate) did not prevent SREs in similar studies. Similarly, clodronate did not prevent SREs in androgen-sensitive metastatic prostate cancer; zoledronic acid is being tested in this setting in CALGB/CTSU 90202. Clodronate also failed to prevent bone metastasis in patients with nonmetastatic prostate cancer. Ongoing pivotal studies are underway to define the role of denosumab in the prevention of disease-related skeletal complications, bone metastases and treatment-related fractures. The completion of these trials over the next few years may herald further evolution in the targeting of osteoclasts in men with prostate cancer.

From a practical standpoint, the optimal duration of zoledronic acid therapy is unknown. Based on clinical practice guidelines for breast cancer and multiple myeloma [45,46], zoledronic acid treatment should continue until treatment-related adverse events or a substantial decline in performance status. The reduction in risk of skeletal complications in men with bone metastases should be weighed against potential adverse effects of zoledronic acid [47]. The most common treatment-related adverse event is an acute phase reaction – a transient influenza-like syndrome of fever, arthralgias and myalgias – beginning within 24 h of treatment. Hypocalcemia is also common but rarely associated with symptoms. Renal toxicity is a recognized and potentially serious adverse effect of zoledronic acid. Zoledronic acid and other bisphosphonates are also associated with increased risk of osteonecrosis of the jaw, especially in patients with 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 the risk of osteonecrosis of the jaw.

Future perspective

The next few years will probably see the completion of several of the aforementioned studies, which may provide new insights into the use of bisphosphonates to prevent bone metastases and skeletal complications, as well as the role for denosumab in both metastatic and non-metastatic settings. An additional study (Amgen Inc. protocol 138) to examine the role of denosumab in treatment-related bone mineral density and fracture risk has accrued 1468 men with prostate cancer who are currently receiving androgen-deprivation therapy. RANKL inhibition may therefore become an important component of care for men at risk of disease- or therapy-related skeletal complications.

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Executive summary

- Bone metastases and skeletal complications are major causes of morbidity in men with prostate cancer.
- Patients with bone metastases have elevated markers of bone resorption, indicative of high osteoclast activity.
- Increased osteoclast activity is independently associated with higher risk of subsequent skeletal complications.
- The only well-examined setting that showed a benefit for bisphosphonates is the use of zoledronic acid in men with androgen-independent prostate cancer and bone metastases.
- Ongoing studies evaluating the use of bisphosphonates or denosumab in the prevention of bone metastases or skeletal complications hold promise for further improvements of supportive care for these patients.
- Additional studies are needed to determine the optimal timing, schedule and duration of bisphosphonate treatment in men with bone metastases.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ: Cancer statistics, 2007. *CA Cancer J. Clin.* 57, 43–66 (2007).
2. Tannock IF, de Wit R, Berry WR *et al.*: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N. Engl. J. Med.* 351, 1502–1512 (2004).
3. Petrylak DP, Tangen CM, Hussain MHA *et al.*: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N. Engl. J. Med.* 351, 1513–1520 (2004).
4. Bubendorf L, Schopfer A, Wagner U *et al.*: Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum. Pathol.* 31, 578–583 (2000).
5. Berruti A, Dogliotti L, Bitossi R *et al.*: Incidence of skeletal complications in patients with bone metastatic prostate cancer and hormone refractory disease: predictive role of bone resorption and formation markers evaluated at baseline. *J. Urol.* 164, 1248–1253 (2000).
   - **Demonstrates an independent association of markers of osteoclast activity with risk of skeletal complications.**
6. Murray RML, Grill V, Crinis N, Ho PWM, Davison J, Pitt P: Hypocalcemic and normocalcemic hyperparathyroidisma in patients with advanced prostate cancer. *J. Clin. Endocrinol. Metab.* 86, 4133–4138 (2001).
7. Roodman GD: Mechanisms of bone metastasis. *N. Engl. J. Med.* 350, 1655–1664 (2004).
   - **Detailed review of the biology of bone metastasis.**
8. Cook RJ, Coleman R, Brown J *et al.*: Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clin. Cancer Res.* 12, 3361–3367 (2006).
9. Maeda H, Koizumi M, Yoshimura K, Yamauchi T, Kawai T, Ogata E: Correlation between bone metabolic markers and bone scan in prostate cancer. *J. Urol.* 157, 539–543 (1997).
10. Clarke NW, McClure J, George NJ: Morphometric evidence for bone resorption and replacement in prostate cnacer. *Br. J. Urol.* 68, 74–80, (1991).
11. Clarke NW, McClure J, George NJ: Osteoblast function and osteomalacia in metastatic prostate cancer. *Eur. Urol.* 24, 286–290 (1993).
12. Boyce BF, Xing L: Biology of RANK, RANKL, and osteoprotegerin. *Arthritis Res. Ther.* 9(Suppl. 1), S1 (2007).
13. Min H, Morony S, Sarosi I *et al.*: Osteoprotegerin reverses osteoporosis by inhibiting endosteal osteoclasts and prevents vascular calcification by blocking a process resembling osteoclastogenesis. *J. Exp. Med.* 192, 463–474 (2000).
14. Mizuno A, Amizuka N, Irie K *et al.*: Severe osteoporosis in mice lacking osteoclastogenesis inhibitory factor/osteoprotegerin. *Biochem. Biophys. Res. Commun.* 247, 610–615 (1998).
15. Blair HC, Teitelbaum SL, Ghiselli R, Gluck S: Osteoclastic bone resorption by a polarized vacuolar proton pump. *Science* 245, 855–857 (1989).

16. Smith MR, McGovern FJ, Zietman AL *et al.*: Pamidronate to prevent bone loss in men receiving gonadotropin releasing hormone agonist therapy for prostate cancer. *N. Engl. J. Med.* 345, 948–955 (2001).
17. Leder BZ, Smith MR, Fallon MA, Lee ML, Finkelstein JS: Effects of gonadal steroid suppression on skeletal sensitivity to parathyroid hormone in men. *J. Clin. Endocrinol. Metab.* 86, 511–516 (2001).
18. Lee Y-P, Schwarz EM, Davies M *et al.*: Use of zoledronate to treat osteoblastic versus osteolytic lesions in a severe-combined-immunodeficient mouse model. *Cancer Res.* 62, 5564–5570 (2002).
19. Carducci MA, Jimeno A: Targeting bone metastasis in prostate cancer with endothelin receptor antagonists. *Clin. Cancer Res.* 12, S6296–S6300 (2006).
20. Rogers MJ, Watts DJ, Russell RGG: Overview of bisphosphonates. *Cancer* 80, 1652–1660 (1997).
21. Asahi H, Mizokami A, Miwa S, Keller ET, Koshida K, Namiki M: Bisphosphonate induces apoptosis and inhibits pro-osteoclastic gene expression in prostate cancer cells. *Int. J. Urol.* 13, 593–600 (2006).
22. Berenson JR, Lichtenstein A, Porter L *et al.*: Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N. Engl. J. Med.* 334, 488–493 (1996).
23. Hortobagyi GN, Theriault RL, Porter L *et al.*: Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N. Engl. J. Med.* 335, 1785–1791 (1996).
24. Rosen LS, Gordon D, Kaminski M, *et al.*: Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a Phase III, double-blind, comparative trial. *Cancer J.* 7, 377–387 (2001).
25. Rosen LS, Gordon D, Tchekmedyian S, *et al.*: Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a Phase III, double-blind, randomized trial – the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J. Clin. Oncol.* 21, 3150–3157 (2003).
26. Saad F, Gleason DM, Murray R *et al.*: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J. Natl Cancer Inst.* 94, 1458–1468 (2002).
•• **The only trial demonstrating a role for bisphosphonate therapy in metastatic prostate cancer, leading to the approval of zoledronic acid for men with prostate cancer and bone metastasis despite first-line hormone therapy.**
27. Diel IJ, Solomayer E-F, Costa SD *et al.*: Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N. Engl. J. Med.* 339, 357–363 (1998).
28. Powles T, Paterson S, Kanis JA *et al.*: Randomized, placebo-controlled trial of clodonate in patients with primary operable breast cancer. *J. Clin. Oncol.* 20, 3219–3224 (2002).
29. Saarto T, Blomqvist C, Virkkunen P, Elomaa I: Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J. Clin. Oncol.* 19, 10–17 (2001).
30. Hiraga T, Williams PW, Ueda A, Tamura D, Yoneda T: Zoledronic acid inhibits visceral metastases in the 4T1/luc mouse breast cancer model. *Clin. Cancer Res.* 10, 4559–4567 (2004).
31. Smith MR, McGovern FJ, Zietman AL *et al.*: Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N. Engl. J. Med.* 345, 948–955 (2001).
32. Michaelson MD, Kaufman DS, Lee H *et al.*: Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J. Clin. Oncol.* 25, 1038–1042 (2007).
33. Schwarz EM, Ritchlin CT: Clinical development of anti-RANKL therapy. *Arthritis Res. Ther.* 9(Suppl. 1), S7 (2007).
34. Bekker PJ, Holloway DL, Rasmusen AS *et al.*: A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. *J. Bone Miner. Res.* 19, 1059–1066 (2004).
• **Demonstrates the efficacy of denosumab (AMG 162), and the advantages of denosumab over osteoprotegerin in eceptor activator of nuclear factor-kB ligand (RANKL) inhibition, leading to continued development of one drug but not the other.**
35. Body J-J, Facon T, Coleman RE *et al.*: A study of the biological receptor activator of nuclear factor-κb ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin. Cancer Res.* 12, 1221–1228 (2006).
36. Lipton A, Steger GG, Figueroa J *et al.*: Randomized active-controlled Phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J. Clin. Oncol.* 25, 4431–4437 (2007).
37. Bekker PJ, Holloway D, Nakanishi A, Arrighi M, Leese PT, Dunstan CR: The effect of a single dose of osteoprotegerin in postmenopausal women. *J. Bone Miner. Res.* 16, 348–360 (2001).
38. Body J-J, Greipp P, Coleman RE *et al.*: A Phase I study of AMGN-0007, a recombinant osteoprotegerin construct, in patients with multiple myeloma or breast carcinoma related bone metastases. *Cancer* 97(Suppl. 3), 887–892 (2003).
39. Saad F, Gleason DM, Murray R *et al.*: Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J. Natl Cancer Inst.* 96, 879–882 (2004).
40. Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO: Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J. Clin. Oncol.* 21, 4277–4284 (2003).
41. Ernst DS, Tannock IF, Winquist EW *et al.*: Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J. Clin. Oncol.* 21, 3335–3342 (2003).
42. Dearnaley DP, Sydes MR, Mason MD *et al.*: A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J. Natl Cancer Inst.* 95, 1300–1311 (2003).
• **Demonstrates a trend ($p > 0.05$ but < 0.10) toward improved bone progression-free and overall survival in men with bone metastases and androgen-sensitive prostate cancer who received clodronate.**
43. Mason MD, Sydes MR, Glaholm J *et al.*: Oral sodium clodronate for nonmetastatic prostate cancer – results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). *J. Natl Cancer Inst.* 99, 765–776 (2007).
44. Smith MR, Kabbinavar F, Saad F *et al.*: Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J. Clin. Oncol.* 23, 2918–1925 (2005).

- **Although the Zometa 704 study examining zoledronic acid in prevention of bone metastasis was aborted, important information about the natural history of nonmetastatic prostate cancer was reported.**

45. Berenson JR, Hillner BE, Kyle RA *et al.*: American Society of Clinical Oncology Clinical Practice Guidelines: the role of bisphosphonates in multiple myeloma. *J. Clin. Oncol.* 20, 3719–3736 (2002).
46. Hillner BE, Ingle JN, Chlebowski RT *et al.*: American Society of Clinical Oncology 2003. Update on the role of bisphosphonates and bone health issues in women with breast cancer. *J. Clin. Oncol.* 21, 4042–4057 (2003).
47. Michaelson MD, Smith MR: Bisphophonates for treatment and prevention of bone metastases. *J. Clin. Oncol.* 23, 8219–9224 (2005).