# Bone complications in prostate cancer: current and future role of bisphosphonates

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## 1. INTRODUCTION

During all disease stages, patients with prostate cancer may suffer from generalised bone loss or localised decreases in bone integrity (for example, at sites of metastatic bone lesions). Notably, low bone mineral density (BMD) is already common in hormone therapy–naïve patients with early-stage prostate cancer [1,2]. In addition to generalised bone loss, osteoblastic bone metastases often appear during prostate cancer progression. These metastases can cause aberrant deposition of the bone matrix (osteogenesis), which triggers both focal bone resorption (osteolysis) adjacent to these sites and generalised increases in osteolysis throughout the skeleton. Higher levels of bone resorption markers have been described in osteoblastic than in osteolytic bone metastases. Patients with all stages of prostate cancer are therefore at risk of bone complications. Increased monitoring and preventive therapies during early disease stages may translate into quality of life (QOL) benefits throughout the continuum of care for patients with prostate cancer [3].

## 2. OSTEOPOROSIS IN MEN WITH PROSTATE CANCER

Even before receiving hormonal therapies or developing bone metastases, patients with prostate cancer are generally at higher risk for fractures as compared with their peers. A recent cross-sectional study of hormone-naïve patients with locally advanced, lymph-node positive, or recurrent prostate cancer found that 31% had osteopoenia in 1 or more skeletal sites. In this patient group, risk factors for osteoporosis—including low dietary calcium intake, hypogonadism, and vitamin D deficiency—were common, suggesting that prostate cancer and osteoporosis may share genetic or environmental risk factors [1,2]. Assessment of BMD could therefore be considered in men as soon as they are diagnosed with prostate cancer—especially if they have known risk factors for osteoporosis.

In this patient population, some benefit may be achieved by ensuring adequate daily calcium and vitamin D intake and by implementing behavioural modifications such as resistance exercises and smoking cessation. Indeed, treatment of vitamin D deficiency in men with prostate cancer can result in a reduction in pain level and an increase in muscle strength. However, behavioural and dietary interventions do not appear to be sufficient to prevent the severe bone loss that can be associated with current therapies for prostate cancer.

### 2.1 Bone Loss Because of Androgen Deprivation

Long-term androgen-deprivation therapy (ADT) has become a common therapeutic option for patients with advanced-stage prostate cancer, and that therapy is usually continued even after hormone-independent disease emerges. Androgen-deprivation therapy is now also commonly administered at an earlier stage and at a younger age in patients who experience biochemical relapse as indicated by elevated levels of prostate-specific antigen (PSA) without evidence of metastatic disease. However, long-term ADT is associated with cumulative adverse effects. Treatment-related sexual impotence, hot flashes, anxiety, depression, gynecomastia, adverse changes in body composition, and accelerated bone loss are common [3–8]. The bone loss resulting from ADT markedly exceeds that observed in postmenopausal women.

In patients with prostate cancer, ADT-induced bone loss is an emerging cause of skeletal morbidity. Men treated with gonadotropin-releasing hormone agonists have significantly lower BMDs and higher levels of biochemical markers of bone metabolism than do eugonadal men. Treated men are also at increased risk for bone fractures. Significant reductions in BMD and increases in bone metabolism are especially profound during prolonged ADT [9–12]. During intermittent therapy, the rate of bone loss is highest during early cycles of therapy. Preliminary investigations suggest that the rate of bone loss decreases during treatment breaks, but that the breaks are insufficient for recovery of bone loss [4,13].

The negative effects of ADT on bones, although initially asymptomatic, can increase the risk of

fracture. Daniell [8] demonstrated a progressive increase in the cumulative fracture incidence over time in men who had received therapeutic orchiectomy. The fracture incidence was significantly worse than in age-matched men who had been castrated. In a recent study, 50% of men who received ADT (chemical castration or maximal androgen blockade) for at least 5 years developed osteoporosis. Moreover, in that population, as compared with age-matched controls, the duration of ADT correlated with risk of osteoporotic hip fracture, with a 20% increase in risk for 1 – 3 years of ADT, a 45% increase in risk for 3 – 5 years of ADT, and a 95% increase in risk for more than 5 years of ADT. A recent study published in the *New England Journal of Medicine* [9] confirmed the significant increase in fracture risk in men on ADT for prostate cancer as compared with men not receiving ADT. All men with prostate cancer who receive any ADT regimen may therefore be at risk not only for developing severe bone loss, but also for fracture [6–10,13]. Baseline BMD evaluations and periodic assessment during ADT may aid in the early identification of bone loss and the timely enactment of intervention strategies.

### 2.2 Prevention of ADT-Induced Bone Loss

Early intervention to prevent bone loss may be key to reducing skeletal morbidity in patients with prostate cancer. Unfortunately, threshold BMD levels that indicate when therapeutic intervention is appropriate have not been clearly established in men, and this lack of clear direction may be an obstacle to the effective care of men on ADT. Clinical trials of antiosteoporotic therapy have largely focused on postmenopausal osteoporosis in women; they might not reflect the relative efficacy of therapies for castrated men. The available treatment options must therefore be considered in the context of prostate cancer.

Current options for preventing postmenopausal osteoporosis include dietary calcium and vitamin supplements, hormonal therapy, and agents that modulate bone metabolism, including calcitonin [11] and bisphosphonates (Table I). However, oral calcium and vitamin D supplementation alone were not sufficient to stop bone loss during ADT in the placebo arms of recent trials of zoledronic acid and pamidronate in men with bone loss in prostate cancer [15,17]. Although other classes of agents that affect bone metabolism may have efficacy in that population, bisphosphonates are the most well-studied and promising ones [12,15,17,20].

The oral bisphosphonate alendronate is currently the only bisphosphonate approved for the treatment of osteoporosis in men. However, the efficacy of oral bisphosphonates in the context of ADT-induced bone loss has yet to be studied. To date, only intravenous therapy with potent nitrogen-containing bisphosphonates has shown efficacy.

Smith *et al.* reported the results of a randomised trial of pamidronate [21]. Compared with no treatment, 60 mg pamidronate every 3 months prevented bone loss over 48 weeks of therapy in men receiving the gonadotropin-releasing hormone agonist leuprolide acetate. Patients treated with pamidronate had significantly higher spinal and hip BMD at 48 weeks. Therefore, intravenous pamidronate prevents bone loss in men undergoing ADT for prostate cancer [15]. However, pamidronate did not significantly increase BMD measurements above baseline values.

Zoledronic acid has also shown efficacy in preserving bone integrity during ADT. In a 12-month, randomised, double-blind, placebo-controlled study in men receiving initial ADT for stage M0 prostate cancer, 4 mg zoledronic acid every 3 months not only prevented cancer treatment–induced bone loss, but also increased BMD above baseline levels at all sites measured. Long-term follow-up of these patients will be necessary to assess fracture rates. Zoledronic acid was well tolerated, and no increase in serum creatinine was observed [17].

Antiandrogen therapies may provide increased specificity, and some appear to be associated with less collateral damage to the skeleton. For example, the nonsteroidal antiandrogen bicalutamide (Casodex: AstraZeneca LP, Wilmington, DE, U.S.A.) binds androgen receptors, competitively inhibiting androgen signals. Bicalutamide typically increases serum levels of both testosterone and estradiol. In a cross-sectional study, patients treated with bicalutamide did not experience bone loss or elevations in bone turnover markers; in contrast, significant changes were detected in patients treated with a gonadotropin-releasing hormone agonist [22].

## 3. SKELETAL MORBIDITY IN MEN WITH METASTATIC PROSTATE CANCER

Most patients with advanced prostate cancer develop bone metastases and require ongoing supportive care. These decreases in skeletal integrity can cause chronic bone pain, pathologic bone fractures, and spinal cord compression. For example, in the placebo control arm of a recent 15-month study in patients with bone metastases secondary to hormone-refractory prostate cancer, more than 40% of patients experienced 1 or more skeletal complications, including pathologic fractures, spinal cord compression, and the need for radiation to bone or for orthopaedic surgery to treat or prevent a fracture. Moreover, median levels of bone pain and of analgesic usage increased during the course of the trial, illustrating the QOL effects of malignant bone disease [19].

Systemic and targeted treatments for prostate cancer may provide palliative or bone protective effects. Radiation therapy (external-beam or bone-seeking radiopharmaceuticals) can temporarily control bone pain in 50% – 90% of treated patients and may prevent bone lesion progression, although repetitive treatments can result in cumulative toxicities. Radia-

TABLE I Bisphosphonates to treat bone loss and skeletal morbidity from bone metastases in patients with prostate cancer

| *Agent* | *Approved indications* | *Treatment of BMD loss during ADT* | *Treatment of bone metastases* |
|---|---|---|---|
| Etidronate | Paget disease only (used off-label for osteoporosis) | Limited efficacy in reducing bone loss [12] | No significant efficacy |
| Clodronate | Bone metastases from breast cancer (not approved in the United States) | NA | Transient (if any) decrease in bone pain [14] |
| Alendronate | Prevention and treatment of osteoporosis in men and women | NA | NA |
| Pamidronate | Treatment of bone lesions in patients with multiple myeloma or breast cancer | Significant reduction of bone loss as compared with placebo [15] | Limited efficacy in reducing skeletal morbidity [16] |
| Zoledronic acid | Treatment of bone metastases from any solid tumor [a] or primary bone lesions from multiple myeloma | Significant increase in BMD as compared with placebo group, and increased BMD over baseline levels [17] | Significant reduction in skeletal morbidity and the risk of skeletal complications [18,19]<br>Significant reduction in bone pain levels, even after 24 months of therapy [19] |

BMD = bone mineral density; ADT = androgen deprivation therapy; NA = not assessed in randomised controlled clinical trials.
[a] Prostate cancer must have progressed during treatment with ≥1 hormonal therapy regimen.

tion therapy is therefore effective for localised bone pain palliation, but its application may be limited in patients with recurrent bone pain [23]. The targeted endothelin receptor antagonist atrasentan (ABT-627: Abbott Laboratories, Abbott Park, IL, U.S.A.) demonstrated promising activity in patients with asymptomatic metastatic hormone-refractory prostate cancer by delaying bone lesion progression in patients treated according to protocol [24]. More recently, docetaxel has demonstrated significant benefits for patients with hormone-refractory prostate cancer, including increases in survival and reductions in pain [25,26]. Further studies are necessary to determine the efficacy of docetaxel-containing regimens in preventing skeletal complications in patients with advanced prostate cancer, and the synergy of that agent with bisphosphonates.

The skeletal complications of bone metastases can be acutely painful and debilitating, and can have a profound effect on QOL. Indeed, Weinfurt *et al.* [3] assessed the effect of skeletal-related events (SREs) on QOL in the subset of 248 patients who experienced 1 or more SREs during a clinical trial in patients with bone metastases from hormone-refractory prostate cancer. Health-related QOL was measured using the Functional Assessment of Cancer Therapy–General and the EURO-EQ-5D questionnaires and the bone pain index interference and intensity scales. In that study, development of an SRE was associated with clinically relevant decrements in multiple domains of health-related QOL. In addition to such QOL decrements, skeletal complications from bone metastases may cause severe pain and debilitation, limit function, and require hospitalisation for treatment, placing greater burdens on patients and caregivers alike. Most metastatic fractures never heal, and mobility can be restored only through surgical procedures, 4% of which lead to mechanical complications [27,28]. Additionally, spinal cord compression occurs in approximately 7% of patients with prostate cancer and can lead to paraplegia if surgical intervention is not immediately provided. More advanced disease and a decline in patient performance have also been shown to negatively affect the QOL of caregivers [3]. Therefore, skeletal complications can have long-term implications for patients and caregivers alike. Delaying or preventing skeletal complications should provide a meaningful benefit for prostate cancer patients and their caregivers alike.

### 3.1 Bisphosphonates to Prevent Bone Complications

Bisphosphonates target bone surfaces and are generally well tolerated for long-term use in patients with cancer, even when administered concomitantly with cytotoxic chemotherapy agents. Early-generation bisphosphonates (for example, etidronate and clodronate) were demonstrated to have limited efficacy in patients with advanced prostate cancer (Table I). As compared with patients receiving placebo, patients ($n = 311$) treated in a randomised clinical trial with daily oral clodronate (2080 mg) for bone pain from prostate cancer showed a trend toward increased bone progression–free survival ($p = 0.066$) and a significantly lower rate of performance status decline [14]. Unfortunately, gastrointestinal toxicity and fluctuations in serum lactate dehydrogenase levels were significantly worse for the oral clodronate group ($p = 0.002$). Intravenous clodronate (1500 mg monthly) was not associated with significant toxicity, but it failed to demonstrate any significant palliative benefit when compared with placebo in phase III clinical testing in men with painful bone metastases from prostate cancer [21].

Later-generation bisphosphonates have greater potency and may have increased efficacy in such a

setting. Ibandronate demonstrated significant pain palliation in a small uncontrolled trial in patients with painful bone metastases from prostate cancer, and pamidronate showed some benefit in that setting, although these benefits failed to reach statistical significance [16,29].

More recently, zoledronic acid (4 mg in a 15-minute infusion every 3 weeks) demonstrated significant objective benefits and received widespread regulatory approval in the setting of painful bone metastases from prostate cancer. In a 24-month placebo-controlled trial in patients with bone lesions from prostate cancer that had progressed during ADT ($n$ = 643), 4 mg zoledronic acid reduced the proportion of patients who experienced skeletal complications by a relative 22% (38% vs. 49% with placebo, $p$ = 0.028). These results are similar are similar to the results obtained in placebo-controlled trials using intravenous bisphosphonates in patients with bone metastases from breast cancer; those trials led to a recommendation for the use of bisphosphonates in the latter setting. Compared with placebo, 4 mg zoledronic acid also decreased the mean annual incidence of skeletal complications by 48% (0.77 events/year vs. 1.47 events/year for placebo, $p$ = 0.005) and significantly prolonged median time to first SRE by more than 5 months as compared with placebo (488 days vs. 321 day, $p$ = 0.009). Furthermore, zoledronic acid (4 mg) significantly reduced the ongoing risk of skeletal complications by 36% in both the 15-month and 24-month datasets [18,19], suggesting that the benefits of therapy were maintained throughout the 24-month study. Throughout the study, as compared with placebo, 4 mg zoledronic acid also consistently reduced bone pain; differences reached statistical significance at the 3-, 9-, 21-, and 24-month time points ($p \leq 0.05$ for each time point) [18].

In addition to objective benefits, bone health maintenance therapies such as bisphosphonates and behavioural modifications (for example, nutrition and exercise) may provide emotional benefits to patients and caregivers alike. Such approaches may provide reassurance that the patient is taking steps to actively prevent or delay the onset of skeletal complications and that treatment decisions will not negatively impact later treatment options [10,20,30].

## 4. CONCLUSIONS AND FUTURE DIRECTIONS

During the course of their disease, patients with prostate cancer develop changes in body composition and function that can negatively impact their health-related QOL. However, effective intervention strategies can prevent some of the changes that these men experience, such as decreased BMD and skeletal complications from their cancers and from the hormonal therapy used to treat them. Effective treatments are now available to quell the focal osteopoenia and severe bone pain that can be triggered when metastatic prostate cancer forms bone lesions. Generalised and focal bone loss can result in severe morbidity during the continuum of disease treatment and progression, and therapeutic intervention should be considered.

As a class, bisphosphonates have also been shown to prevent cancer treatment–induced bone loss in patients receiving long-term androgen deprivation. Pamidronate has demonstrated some efficacy in preventing BMD decreases in patients receiving ADT, and zoledronic acid has been shown to increase BMD during ADT. Furthermore, bisphosphonates are known to palliate bone pain, and in a long-term, randomised, phase III trial, zoledronic acid recently became the first bisphosphonate to demonstrate (as compared with placebo) statistically significant reductions in bone pain in patients with hormone-refractory prostate cancer. In the latter trial, zoledronic acid also significantly reduced skeletal morbidity in patients with advanced hormone-refractory prostate cancer.

In addition to preserving BMD and preventing skeletal morbidity from bone metastases in patients with prostate cancer, preclinical evidence suggests that bisphosphonate treatment of early-stage prostate cancer may reduce the incidence of bone metastases [31]. The potential of bisphosphonates to prevent bone metastasis is currently being investigated in clinical trials in patients with breast cancer, prostate cancer, renal cell cancer, and other solid tumours. Furthermore, preservation of BMD during the early stages of prostate cancer may reduce the risk of skeletal complications that typically occur when prostate cancer metastasises to bone—although further studies are necessary. Therefore, bone-maintenance therapies in patients with early-stage or advanced cancer may reduce skeletal morbidity throughout the continuum of care for patients with prostate cancer.

## 5. REFERENCES


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