Bone loss in prostate cancer: evaluation, treatment and prevention

Fred Saad, MD

Department of Surgery/Urology, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, Quebec, Canada

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Modern medicine offers multiple treatment options to prolong the survival of patients with prostate cancer. However, in the absence of adequate supportive care, the systemic effects of prostate cancer and therapies such as androgen deprivation therapy (ADT) can undermine skeletal integrity, resulting in skeletal complications. Skeletal morbidity contributes to the erosion in quality of life in patients with prostate cancer. These patients are at risk for fractures from cancer treatment-induced bone loss and, later on, pathologic fractures from bone metastases, which may occur during the progression of prostate cancer. Several supportive care options are available to prevent generalized and focal bone loss, including calcium and vitamin D supplements and bisphosphonates. Oral calcium and vitamin D supplementation alone, however, appears to be insufficient to prevent bone loss during ADT. Bisphosphonates may be beneficial in preventing bone loss and eventually reducing skeletal morbidity due to prostate cancer and ADT.

Key Words: bisphosphonates, prostate cancer, bone loss

Introduction

Men who are diagnosed with advanced prostate cancer often receive androgen deprivation therapy (ADT) at some time during the disease. Prostate cancer can be considered a chronic disease in many patients with non-metastatic prostate cancer since the disease may progress for over 10 years in most cases. In this context, the effects of disease symptoms and ongoing treatment effects on quality of life (QOL) are important considerations.

During all disease stages, patients with prostate cancer may suffer from generalized or focal bone loss. Of note, low bone mineral density (BMD) is already common in hormone therapy-naïve patients with prostate cancer.[1,2] Tumor-induced bone loss in prostate cancer and non-cancer related osteoporosis share many predisposing factors. Disease-related factors such as perturbations in serum ion and hormone levels and treatment-related effects on bone metabolism—all of which can accelerate loss in BMD— could also contribute to the prevalence of low BMD (osteopenia and osteoporosis) in these patients. Therefore, patients with all stages of prostate cancer are at risk for developing skeletal complications from bone loss. Increased monitoring and preventive therapies during early stages of prostate cancer may translate into QOL benefits throughout the continuum of care for patients with prostate cancer.

Address correspondence to Dr. Fred Saad, Department of Surgery/Urology, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, 1560 Rue Sherbrooke East, Montréal, Quebec H2L 4M1 Canada

Osteoporosis in men with prostate cancer

Managing the primary malignancy is essential to prolonging survival in men with prostate cancer. However, management of the secondary effects of prostate cancer therapies and the cancer itself are essential for preserving QOL throughout the patient's life. Asymptomatic decreases in BMD during cancer treatment can lead to an increased risk of skeletal

morbidity.[3] This "silent" threat increases, especially with prolonged hormonal therapy and with disease progression, and the potential effects of skeletal complications on the patient's life are often underestimated by both the patient and the treating physician.

Historically, the majority of osteoporosis research has focused on postmenopausal women and many guidelines and algorithms have been developed to prevent and treat osteoporosis following menopause. Recently it has been recognized that the prevalence of osteoporosis and osteoporotic fractures in men is increasing, especially in the elderly. The National Osteoporosis Foundation estimates that 2 million American men have osteoporosis, and the prevalence will increase during the next 2 decades, as the nation ages. Currently, approximately 30% of all osteoporotic hip fractures occur in men,[4] yet osteoporosis in men is both underdiagnosed and undertreated.[5] Although osteoporosis may be more prevalent in postmenopausal women, men generally have a poorer prognosis following osteoporotic fractures. Proper diagnosis and treatment are needed. Current strategies to prevent osteoporotic fractures include hormonal therapies and agents that affect bone metabolism (fluoride, calcitonin, and bisphosphonates), but the majority of osteoporosis research with these agents has focused on postmenopausal women.

Osteoporotic fractures significantly decrease health-related QOL in both men and women. Recently, the Canadian Multicentre Osteoporosis Study of community-dwelling men and women > 50 years of age (n = 4816) reported that osteoporotic main fractures (clinically recognized hip, spine, wrist/forearm, pelvis, or rib site fractures) were correlated with significant decreases in health-related QOL parameters, including physical functioning (–4.0; 95% confidence interval [CI] = –6.0, –2.0) and role-physical functioning domains (–5.8; 95% CI = –9.5, –2.2).[6] Additionally, men who experienced osteoporotic hip fractures had especially profound decreases in their role-physical domain scores (–35.7; 95% CI = –60.4, –11.1).

Osteoporotic fractures can occur at any skeletal site and can impact multiple aspects of a patient's life. Vertebral fractures are the most common form of osteoporotic fracture and are usually the first to occur in both men and women. Although vertebral fractures are often underdiagnosed and undertreated, they can be an underlying cause of back pain, posture changes, height and stature loss, and functional impairment.[7] The resulting vertebral deformity can restrict lung volume, cause sleeping and eating disturbances (e.g. reflux esophagitis), and decrease balance and mobility. Osteoporotic hip fractures are an especially serious complication, and the morbidity associated with hip fractures is generally more severe in men than in women.[8] Indeed, a retrospective analysis found that 16% of men did not survive for more than 30 days after a hip fracture, and roughly 60% of the men who survived did so with impaired mobility, often requiring a cane or walker. Furthermore, hip fractures in men result in considerable increases in healthcare costs, as 79% of men require a nursing home, intermediate care facility, or at-home attendant care after a hip fracture. Consequently, men are likely to account for a substantial portion of the direct medical costs for treating osteoporotic fractures. Therefore, osteoporotic fractures can decrease both survival and QOL and can increase healthcare costs for men.

Even before receiving hormonal therapies or developing bone metastases, patients with prostate cancer are generally at higher risk of developing osteoporotic fractures compared with their peers. A recent cross-sectional study of hormone-naive patients with locally advanced, lymph node positive, or recurrent prostate cancer found that 31% of patients had osteopenia in one skeletal site, and 63% of men would have been diagnosed with osteoporosis based on their lumbar spine BMD. In this patient group, risk factors for osteoporosis, including low dietary calcium intake, hypogonadism, and vitamin D deficiency were common, thereby suggesting that prostate cancer and osteoporosis may also share genetic or environmental risk factors. Based on these findings, serial screening of BMD should be considered in men with prostate cancer starting ADT.

Cancer treatment-induced bone loss

Androgen deprivation therapy (ADT) is the standard therapy for patients with locally advanced and metastatic prostate cancer or patients with recurrence following local therapy. Long-term ADT (continuous or intermittent) has become state-of-the-art therapy for patients with advanced stage prostate cancer, and ADT is often continued even after hormone-independent disease emerges. ADT is now also commonly administered to patients who have biochemical relapse, as indicated by elevated PSA levels but no evidence of metastatic disease. However, chronic exposure to ADT is associated with cumulative adverse effects. Treatment-related sexual impotence, hot flushes, anxiety, depression, gynecomastia, body composition disorders,[9] as well as accelerated bone loss are common.

The bone loss resulting from cancer treatment (ADT) has been shown to markedly exceed that observed in postmenopausal women.[10] Furthermore, a prevalent androgen deprivation-associated syndrome (characterized by weight gain, anemia, memory difficulties, and severe bone and joint pain) has been recognized in prostate cancer patients treated with ADT. Declines in physical function (urinary, sexual, and general health) following surgery, radiotherapy, or disease progression, and these adverse effects of hormonal therapy can all negatively impact emotional well-being.

Cancer treatment-induced bone loss (CTIBL) is an emerging cause of osteoporosis and skeletal morbidity in patients with prostate cancer. Radiation and chemotherapy may have direct effects on bone metabolism,[11] and therapies that suppress hormonal signaling, such as ADT, trigger decreases in BMD. Significant decreases in BMD and increases in bone metabolism are especially profound during prolonged ADT.[12-15] Clinical trials of intermittent ADT, which aims to reduce the cost and chronic effects of ADT,[16] have also documented BMD decreases. The rate of bone loss was highest during early cycles of therapy.[17,18] The negative effects of ADT on bones, though initially asymptomatic, can lead to serious sequelae. For example, patients treated with ADT suffer an increased risk of fractures,[19,20] and this risk increases as the length of therapy increases.[21] Daniell et al[12] demonstrated a progressive increase over time in the cumulative fracture incidence in men who had been treated with therapeutic orchiectomy. The fracture incidence was significantly worse than in age-matched men who had not received this therapy. Recently, prolonged ADT was reported to significantly increase the risk of osteoporotic hip fractures.[13] Therefore, all men with prostate cancer who receive any ADT regimen should be considered at risk for developing severe bone loss from CTIBL and should be treated accordingly, with regular BMD evaluations and the enactment of intervention strategies where indicated.

Prevention of cancer treatment-induced bone loss

Early intervention to prevent bone loss is critical to reduce skeletal morbidity in patients with prostate cancer. Unfortunately, the 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 with CTIBL. Clinical trials of antiosteoporotic therapy have largely focused on postmenopausal osteoporosis in women, and therefore might not reflect the relative efficacy of therapies for CTIBL in men. Therefore, the available treatment options must be considered in the context of prostate cancer. Current options for preventing CTIBL include dietary calcium and vitamin supplements, hormonal therapy, and agents that modulate bone metabolism, including calcitonin and bisphosphonates Table 1.[22-29] However, oral calcium and vitamin D supplementation alone were not sufficient to stop bone loss during ADT in the placebo arms of recent CTIBL trials of zoledronic acid and pamidronate in men with prostate cancer.[28,29] Recent evidence suggests that the absorption of calcium and vitamin D may be impaired in patients with prostate cancer.[30] Although other agents that affect bone metabolism may have efficacy in this population, bisphosphonates are the most well-studied and promising agents.[31]

The oral bisphosphonate alendronate is currently the only bisphosphonate that is widely approved for the treatment of non-cancer–associated osteoporosis in men. However, oral alendronate showed limited efficacy in preventing nonvertebral fractures in hypogonadal men. Therefore, alendronate may not be potent enough to effectively manage BMD decreases that occur during long-term ADT. Alendronate has not been specifically approved for the treatment of CTIBL.[32] Further, one retrospective analysis of alendronate-treated women reported a 60% increase in outpatient visits or hospital admissions for acid-related upper gastrointestinal disorders (ARD) compared with the rate of a control population of patients. The risk of ARD increased with patient age and with the concurrent use of nonsteroidal anti-inflammatory drugs.[33] Therefore, the use of alendronate or other oral bisphosphonates in men with prostate cancer may be complicated by age-related or treatment-related gastrointestinal sensitivities. Intermittent cyclic therapy with the oral bisphosphonate etidronate has been tested in patients receiving ADT and has also demonstrated limited efficacy in preventing decreases in BMD.[25]

Intravenous (IV) therapy with potent nitrogen-containing bisphosphonates has shown promising efficacy. The IV bisphosphonates pamidronate and zoledronic acid offer several advantages over oral bisphosphonates.[26,27,34] In contrast with oral bisphosphonates, which are typically administered daily or weekly, these IV bisphosphonates can be administered once every 3 months for the prevention of CTIBL in men, and both of these agents have shown different levels of activity in this setting.

TABLE 1. **Therapies to treat bone loss and skeletal morbidity from bone metastases in patients with prostate cancer**

Agent	Type	Approved indications	Treatment of BMD loss during ADT	Treatment of bone metastases
Calcium and vitamin D	Supplement	Osteoporosis (variable efficacy)	NA	NA
Estrogen-based therapy	Hormonal	Postmenopausal osteoporosis	BMD preserved (low tolerability)	NA
Calcitonin	Bone metabolism hormone	Postmenopausal osteoporosis	Bone resorption reduced but not normalized	NA
Etidronate	Bisphosphonate (osteolysis inhibitor)	Paget's disease only (used off-label for osteoporosis)	Limited efficacy in reducing bone loss	No significant efficacy
Clodronate	Bisphosphonate	Bone metastases from breast cancer (not approved in United States)	NA	Transient (if any) decrease in bone pain
Alendronate	Bisphosphonate	Prevention and treatment of osteoporosis in men and women	NA	NA
Pamidronate	Bisphosphonate	Treatment of bone lesions in patients with multiple myeloma or breast cancer	Significant reduction of bone loss compared with placebo	Limited efficacy in reducing skeletal morbidity
Zoledronic acid	Bisphosphonate	Treatment of bone metastases from any solid tumor* or primary bone lesions from multiple myeloma	Significant increase in BMD compared with placebo group, and increased BMD over baseline levels	Significantly reduced skeletal morbidity and the risk of skeletal complications Significant reductions in bone pain levels, even after 24 months of therapy**

ADT = Androgen deprivation therapy; NA = Not assessed in randomized controlled clinical trials.
*Prostate cancer must have progressed during treatment with ≥ 1 hormonal therapy regimen.
**Compared with placebo control.

In an early study of a single infusion of pamidronate (90 mg) in men receiving ADT, serum levels of metabolic markers of osteolysis were decreased for at least 6 months compared with the placebo control group.[35] Smith et al[26] subsequently reported the results of a placebo-controlled randomized trial of pamidronate. Compared with placebo, a 2-hour infusion of 60 mg pamidronate every 3 months diminished BMD loss over 48 weeks of therapy in men receiving the gonadotropin-releasing hormone agonist leuprolide. Patients treated with pamidronate had significantly higher spinal and hip BMD at 48 weeks. Therefore, IV pamidronate prevents CTIBL in the hip and spine of men undergoing ADT for prostate cancer. However, pamidronate did not significantly increase BMD measurements above

baseline values.[36]

In contrast with earlier bisphosphonates, zoledronic acid, the most potent new generation bisphosphonate, has recently been shown to effective for the treatment of bone metastases in patients with hormone-refractory prostate cancer in that it significantly reduces skeletal complications.[29] Zoledronic acid has also shown efficacy in preventing CTIBL during ADT: in a 12 month, randomized, double-blind, placebo-controlled study in men receiving initial ADT for stage M0 prostate cancer (n = 106), zoledronic acid (4 mg via 15-minute infusion every 3 months) not only prevented CTIBL but actually increased BMD compared with baseline levels at all sites measured.[28] The improvement in BMD achieved with zoledronic acid was especially profound in the lumbar spine ($P < .001$). The trial was of insufficient duration to detect differences in fracture rates between treatment groups. However, improvements in BMD might be expected to delay the onset or decrease the incidence of skeletal complications at later stages of disease progression. Long-term follow-up of these patients will be necessary to assess the effects on fracture rates. Zoledronic acid was well tolerated, and no significant increase in serum creatinine was reported in any patients at any time during the trial.

Newer anti-androgen therapies may provide increased specificity, thereby reducing collateral damage to the skeleton. For example, the nonsteroidal antiandrogen bicalutamide (Casodex, AstraZeneca) binds androgen receptors, competitively inhibiting androgen signals. Bicalutamide typically increases serum levels of both testosterone and estradiol. In a 6-month study, patients treated with bicalutamide did not experience bone loss or elevations in serum or urinary levels of bone turnover markers, in contrast with the significant changes detected in patients treated with a gonadotropin-releasing hormone agonist.[37] Additional follow-up is needed to assess long-term effects and limitations of bicalutamide. Although bicalutamide (150 mg) is active in patients with nonmetastatic prostate cancer, bicalutamide monotherapy is less effective than ADT in patients with bone metastases.

There are data to suggest that preservation of BMD in men may correlate with increased survival. In addition to the increased risk of bone fractures, below-average BMD was shown to correlate with an increased risk of mortality in a population of men 55 years of age, even when risk factors such as diabetes, smoking, and prior hip fractures were taken into account.[38] Therefore, bisphosphonate therapy to increase BMD may be associated with a survival benefit.

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. Effective treatments are now available to quell the focal osteopenia and severe bone pain that can be triggered when metastatic prostate cancer forms bone lesions. Generalized 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, IV bisphosphonates have also been shown to prevent CTIBL in patients receiving long-term ADT. Pamidronate has demonstrated some efficacy in preventing BMD decreases in patients receiving ADT,[26] but zoledronic acid has been shown to increase BMD during ADT. Additionally, zoledronic acid reduces skeletal morbidity in patients with advanced hormone-refractory prostate cancer.[28,29]

In addition to preserving BMD and preventing skeletal morbidity from bone metastases in patients with prostate cancer, the potential of bisphosphonates to prevent bone metastasis is currently being investigated. Furthermore, preservation of BMD during early stages of prostate cancer may reduce the risk of skeletal complications that typically occur when prostate cancer metastasizes to bone, though further studies are necessary to examine the effects of treatment history on patients with advanced disease. Therefore, bisphosphonate therapy in early-stage patients and patients with advanced cancer may reduce skeletal morbidity throughout the continuum of care for patients with prostate cancer.

Suggestions for patients going on to ADT

Ensure adequate Calcium and Vitamin D intake and consider doing a baseline BMD.

Suggestions according to the result of BMD

Normal limits (-1 to 1) - consider repeat BMD in 1 year.

Osteopenic (-1 to -2.5) - consider bisphosphonate use and repeat BMD 6-12 months especially if no bisphosphonate prescribed.

Osteoporotic (less than -2.5) - bisphosphonate recommended to prevent osteoporotic fracture and repeat BMD in 6-12 months. □

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