Bone health in men with prostate cancer: diagnostic and therapeutic considerations

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SAAD F, PERROTTE P, BENARD F, MCCORMACK M, KARAKIEWICZ PI. Bone health in men with prostate cancer: diagnostic and therapeutic considerations. The Canadian Journal of Urology. 2005;12(Supplement 2):9-15.

With current treatments, men usually survive many years after being diagnosed with prostate cancer. However, the systemic effects of prostate cancer and therapies such as androgen deprivation therapy (ADT) can undermine skeletal integrity, resulting in skeletal complications that may erode quality of life (QOL). Prostate cancer patients are at risk for fractures from cancer treatment-induced bone loss. In addition, they are also at risk for pathologic fractures, severe bone pain, and other sequelae from bone metastases, which almost invariably occur during the progression of prostate cancer. This review investigates the incidence and pathophysiology of bone loss and skeletal morbidity in prostate cancer patients and reviews available treatment options for maintaining skeletal health throughout the continuum of care for these patients. Several supportive interventions are available to prevent generalized and localized 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. New generation bisphosphonates such as zoledronic acid can prevent bone loss for patients on ADT and can reduce skeletal morbidity for those with bone metastases.

Key Words: bone health, prostate cancer, ADT

Introduction

During all disease stages, patients with prostate cancer may suffer from generalized bone loss or localized decreases in bone integrity (e.g. at sites of metastatic bone lesions). Of note, low bone mineral density (BMD) is already common in hormone therapy-naive patients with early stage prostate cancer.[1] In addition to general bone loss, osteoblastic bone metastases often appear during prostate cancer progression and can cause aberrant deposition of the bone matrix (osteogenesis), which triggers both focal bone resorption (osteolysis) adjacent to these sites and generalized increases in osteolysis throughout the skeleton. Higher levels of bone resorption markers have been described in osteoblastic versus osteolytic bone metastases. Therefore, patients with all stages of prostate cancer are at risk of 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.

Osteoporosis in men with prostate cancer

Treating or monitoring the primary malignancy is essential to prolong survival in men with prostate cancer. However, management of the side 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. This "silent" threat increases, especially

Acknowledgement

Dr. Fred Saad is a member of the advisory boards and has had research funded by Novartis Pharmaceuticals Canada Inc., sanofi-aventis, Abbott Laboratories Ltd., AstraZeneca Canada Inc., AMGEM, Pfizer Canada Inc., and Merck Frosst Canada Ltd.

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with prolonged ADT and with disease progression, and the skeletal complications that may occur have significant negative impacts on multiple aspects of QOL.[2] Historically, the majority of osteoporosis research has focused on postmenopausal women. Recently, however, it has been recognized that osteoporosis and associated morbidities are increasing in men. The National Osteoporosis Foundation estimates that 2 million American men have osteoporosis, and the prevalence is likely to increase as the population ages. Currently, approximately 30% of all osteoporotic hip fractures occur in men, yet osteoporosis in men is both underdiagnosed and undertreated. Moreover, men generally have a poorer prognosis than women following these fractures. Proper diagnosis and treatment are needed. Current prevention strategies suggest the use of agents that affect bone metabolism (e.g. parathyroid hormone, calcitonin, and bisphosphonates), but the majority of research with these agents has focused on postmenopausal women.

Fractures significantly decrease health-related QOL in both men and women. 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. The resulting vertebral deformities can restrict lung volume, cause sleeping and eating disturbances (e.g. reflux esophagitis), and decrease balance and mobility. Hip fractures are an especially serious complication, and their associated morbidity is generally more severe in men than in women. Indeed, a retrospective analysis found that 16% of men died within 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, 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.[3,4]

Even before receiving hormonal therapies or developing bone metastases, patients with prostate cancer are generally at higher risk for 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 ≥ 1 skeletal site. 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.[1] Therefore, BMD assessment could 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, ensuring adequate daily calcium and vitamin D intake and implementing behavioral modifications, such as resistance exercises and quitting smoking, may provide some benefits. Indeed, treatment of vitamin D deficiency in men with prostate cancer can result in decreases in pain levels and increases in muscle strength. However, behavioral 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.[5,6]

Cancer treatment-induced bone loss

Long-term ADT has become a common therapy for patients with advanced-stage prostate cancer, and ADT is usually continued even after hormone-independent disease emerges. Androgen-deprivation therapy is now also commonly administered at an earlier stage and younger age to patients who have biochemical relapse, as indicated by elevated PSA levels but no 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.[5]

The bone loss resulting from ADT markedly exceeds that observed in postmenopausal women. Furthermore, a prevalent androgen deprivation-associated syndrome (characterized by weight gain, anemia, and memory difficulties) has been recognized in prostate cancer patients. Declines in physical function (e.g. urinary and sexual) following surgery or radiotherapy, the adverse side effects of ADT, and the morbid effects of disease progression can all negatively impact QOL.

Cancer treatment-induced bone loss (CTIBL) is an emerging cause of bone loss and skeletal morbidity in patients with prostate cancer. Radiation and chemotherapy may have direct effects on bone metabolism, and therapies that suppress hormonal signaling, such as ADT, trigger decreases in BMD. For example, men treated with gonadotropin-releasing hormone agonists have significantly lower BMD and higher levels of biochemical markers of bone metabolism compared with eugonadal men and are

at an increased risk for bone fractures. Significant decreases in BMD and increases in bone metabolism are especially profound during prolonged ADT. 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 breaks are insufficient for recovery of bone loss.[7,8] Therefore, ongoing BMD assessments have been recommended during intermittent ADT. Further intervention for bone loss may be needed.[9,10]

The negative effects of ADT on bones, though initially asymptomatic, can increase the risk of fractures. Daniell[11] et al demonstrated a progressive increase over time in the cumulative fracture incidence in men who had received therapeutic orchiectomy. The fracture incidence was significantly worse than in age-matched men who had not received orchiectomy. In a recent study, 50% of men who received ADT (chemical castration or maximal androgen blockade) for at least 5 years developed osteoporosis. Moreover, the duration of ADT correlated with risk of osteoporotic hip fractures in this population compared with age-matched controls, with a 20% increase in risk for 1 to 3 years of ADT, a 45% increase in risk for 3 to 5 years of ADT, and a 95% increase in risk for more than 5 years of ADT. Therefore, all men with prostate cancer who receive any ADT regimen may be at risk for developing severe bone loss from CTIBL.[12] Baseline BMD evaluations and periodic assessment during ADT may aid in the early identification of bone loss and the timely enactment of intervention strategies.

Prevention of prostate 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 postmenopausal osteoporosis include dietary calcium and vitamin supplements, hormonal therapy, and agents that modulate bone metabolism—including calcitonin and bisphosphonates[7,8,12-18] Table 1. 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. Although other agents that affect bone metabolism may have efficacy in this population, bisphosphonates are the most well-studied and promising agents.[16,18]

The oral bisphosphonate alendronate is currently the only bisphosphonate approved for the treatment of osteoporosis in men. However, the efficacy of oral alendronate has not been investigated in men with castrate-level testosterone. Moreover, the use of alendronate or other oral bisphosphonates in men with prostate cancer may be complicated by age-related or treatment-related gastrointestinal sensitivities. Etidronate, another oral bisphosphonate, has been investigated in patients with early prostate cancer but has demonstrated limited efficacy.

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. 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.[16,18]

Smith et al reported the results of a randomized trial of pamidronate. Compared with no treatment, a 2-hour infusion of 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, 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.

Zoledronic acid has also shown efficacy in preventing the negative effects on bone from CTIBL and improving BMD 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 increased BMD above baseline levels at all sites measured. The improvement was especially profound in the lumbar spine ($P < .001$). No significant differences in fracture rates were detected, consistent with the short duration of the trial and the low incidence of events in this patient population.

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 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†

BMD = Bone mineral density; 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.

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 fracture rates. Zoledronic acid was well tolerated, and no significant increase in serum creatinine was observed.[18]

Anti-androgen 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, Del) 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 with the significant changes detected in patients treated with a gonadotropin-releasing hormone agonist.[20] Although high-dose bicalutamide

(150 mg) is active in patients with nonmetastatic prostate cancer, bicalutamide monotherapy is less effective than ADT in patients with bone metastases.[21]

Preservation of BMD 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. Further studies are needed to investigate the long-term benefits of bone health maintenance in patients with early-stage prostate cancer and to optimize bone loss prevention strategies.

Skeletal morbidity in men with advanced prostate cancer

The majority of patients with advanced prostate cancer develop bone metastases and require ongoing supportive care. Resulting 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 HRPC, more than 40% of patients experienced ≥ 1 skeletal complication, including pathologic fractures, spinal cord compression, and the need for radiation to bone or orthopedic surgery to treat or prevent a fracture. Moreover, median bone pain levels and 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% to 90% of treated patients and may prevent bone lesion progression, although repetitive treatments can result in cumulative toxicities. Therefore, radiation therapy is effective for bone pain palliation, but its application may be limited in patients with recurrent bone pain.[22-24] The targeted endothelin receptor antagonist atrasentan (ABT-627; Abbott Laboratories, Abbott Park, Ill) demonstrated promising activity in patients with prostate cancer in early clinical testing, including the prevention or delay of bone lesion progression in patients treated per protocol.[25] More recently, docetaxel has demonstrated significant benefits for patients with HRPC, including increases in survival and decreases in pain.[26,27] Further studies are necessary to determine the efficacy of docetaxel-containing regimens in preventing skeletal complications in patients with advanced prostate cancer.

The skeletal complications of bone metastases can be acutely painful, debilitating, and can have a profound effect on QOL. Indeed, Weinfurt et al assessed the effect of SREs on QOL in the subset of 248 patients who experienced ≥ 1 SRE during a clinical trial in patients with bone metastases from hormone-refractory prostate cancer (HRPC).[28,29] Health-related quality of life was measured using the Functional Assessment of Cancer Therapy-General (FACT-G) and EURO-EQ-5D questionnaires and the bone pain index interference and intensity scales. The development of an SRE was associated with clinically relevant decrements in multiple domains of health-related quality of life. In addition to QOL decrements, skeletal complications from bone metastases may cause severe pain and debilitation, limit function, and require hospitalization for treatment, placing greater burdens on patients and caregivers alike.[2] The majority of metastatic fractures never heal, and mobility can only be restored through surgical procedures, 4% of which lead to mechanical complications. Additionally, spinal cord compression occurs in approximately 7% of patients with prostate cancer and can lead to paraplegia if surgical intervention is not performed immediately. More advanced disease and a decline in patient performance have also been shown to negatively impact caregivers' QOL.[2] 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.

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 (e.g. etidronate and clodronate) have demonstrated limited efficacy in patients with advanced prostate cancer Table 1. Patients with bone pain from prostate cancer treated with daily oral clodronate (2080 mg) had a trend towards increased bone progression-free survival (P = .066) and a significantly lower rate of performance status decrease compared with placebo in a randomized clinical trial (N = 311). Unfortunately, gastrointestinal toxicity and fluctuations in serum lactate dehydrogenase levels were significantly worse for oral clodronate compared with placebo (P = .002).[30] Intravenous clodronate (1500 mg/month) was not associated with significant toxicity, but failed to demonstrate any significant palliative benefits compared with placebo in phase III clinical testing in men with painful bone metastases from prostate cancer.[31] Later-generation

bisphosphonates have greater potency and may have increased efficacy in this 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 this setting, although these benefits failed to reach significance.[32]

More recently, zoledronic acid (4 mg via 15-minute infusion every 3 weeks) demonstrated significant objective benefits and received widespread regulatory approval in this setting. 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% versus 49% with placebo; $P = .028$), and the difference remained significant ($P < .05$) when asymptomatic fractures were excluded from the analysis. These results are similar are similar to those obtained in placebo controlled trials using IV bisphosphonates in patients with bone metastases from breast cancer, which have lead to the recommended use of bisphosphonates in that setting. Compared with placebo, 4 mg zoledronic acid also decreased the mean annual incidence of skeletal complications by 48% (0.77 versus 1.47 events/year for placebo, $P = .005$) and significantly prolonged median time to first SRE by more than 5 months compared with placebo (488 versus 321 days for placebo; $P = .009$). Zoledronic acid (4 mg) also significantly reduced the ongoing risk of skeletal complications by 36% in both the 15- and 24-month data sets, suggesting that the benefits of therapy were maintained throughout the 24-month study. Throughout this study, zoledronic acid (4 mg) also consistently reduced bone pain compared with placebo, with differences reaching significance at 3-, 9-, 21-, and 24-month time points ($P \leq .05$ for each).[33]

In addition to objective benefits, bone health maintenance therapies such as bisphosphonates and behavioral modifications (e.g. nutrition and exercise) may provide emotional benefits to patients and caregivers alike. These approaches may provide reassurance that they are taking steps to actively prevent or delay the onset of skeletal complications and that their treatment decisions will not negatively impact their later treatment options.[15,34]

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 the hormonal therapy used to treat them. 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, 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 zoledronic acid recently became the first bisphosphonate to demonstrate statistically significant reductions in bone pain compared with placebo in patients with HRPC in a long-term, randomized, phase III trial. In this trial, zoledronic acid also significantly reduced skeletal morbidity in patients with advanced HRPC.

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.[35] 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 tumors. 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, 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. □

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