



Preventing bone complications in advanced prostate cancer

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ABSTRACT

The diagnosis and treatment of prostate cancer have steadily been improving since the late 1980s. However, clinicians still confront a large group of men developing disease metastatic to bone. Adequate control of bone complications plays a fundamental role in achieving control of symptoms and quality of life in this group. Androgen deprivation therapy, the standard treatment for advanced prostate cancer, increases the risk of various complications, including bone disease. This review addresses the prevention of bone complications related not only to prostate cancer metastases but also to impaired bone integrity caused by androgen deprivation therapy.

KEY-WORDS

Prostate cancer, bone metastases, skeletal complications

1. INTRODUCTION

Prostate cancer (pca) is the most prevalent malignancy and the third leading cause of cancer-related death among men in Canada. In facing a disease with heterogeneous clinical presentation, it needs to be kept in mind that 10% of patients will initially present with bone metastases and that nearly all patients who die from pca have skeletal involvement¹. In advanced cancer, more than half the patients with bone metastases develop some form of skeletal complication such as severe pain, fracture, spinal cord compression, marrow failure, or hypercalcemia. Moreover, more than 70% of all patients are diagnosed between 60 and 80 years of age, making adaptation in bone structure an important element in the pathophysiology of bony complications².

Much interest has been directed toward a better understanding of the biology and clinical pathophysiology of bony complications³. In this review, we report the current strategies and advances for preventing bone complications of advanced pca. A computer-assisted search of the PubMed database using the keywords "prostate cancer," "bone metastases," "androgen

deprivation therapy," "skeletal complications," and "bisphosphonates" identified relevant papers. Additional citations from those papers were also selected. Only papers published in English were chosen.

2. DISCUSSION

2.1 Pathophysiology of Bone Metastases

Bone metastases from pca most commonly affect the axial skeleton, but they can present at any other osseous site, from distal extremities to the skull. Once involved, the bone reveals activation of osteoblasts and osteoclasts. This activation will ultimately cause formation of weak, sclerotic bone⁴. The precise mechanism to explain this process is unclear. The several current theories include molecular mechanisms of linkage between tumour and bone cells through adhesion molecules (for example, selectins, integrins, and cadherins). This interaction involving tumour cells and bone marrow sinusoids seems essential for early metastatic development⁵. Furthermore, several proteins in the bone environment promote local tumour progression. Finally, the cellular component of bone plays a determinant role supporting metastasis viability, secreting growth factors and components of extracellular matrix. The RANKL factor (receptor activator of nuclear factor κ B ligand) produced by osteoblasts is currently the focus of several studies. Briefly, RANKL works by activating osteoclasts, increasing bone resorption, making RANKL a promising therapeutic target⁶ (Figure 1).

2.2 Bone Complications Induced by Androgen Deprivation Therapy in Patients with Advanced Prostate Cancer

Androgen deprivation therapy (ADT) remains the first-line treatment for advanced pca. However, the principal forms of ADT decrease circulating testosterone to castrate levels through bilateral orchiectomy or gonadotropin-releasing hormone agonists or antagonists, resulting in significant increases in bone resorption and an elevated risk of osteoporotic fractures⁷.

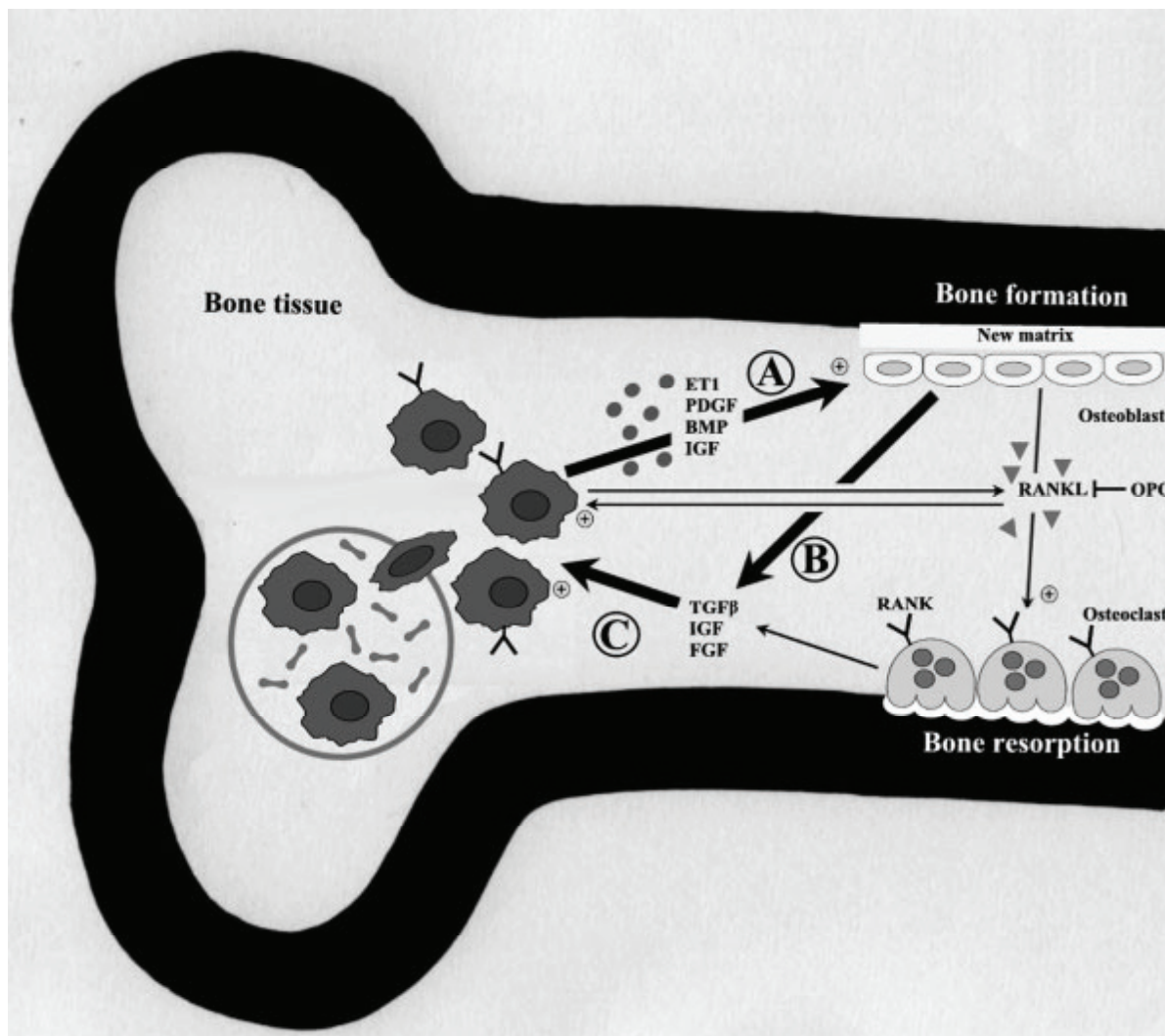


FIGURE 1 The “vicious cycle” of osteoblastic metastases as described by Ibrahim and colleagues, 2010³. (A) Prostate cancer cells secrete osteogenic growth factors, activating osteoblasts to deposit new bone matrix. (B) Osteoblasts secrete a range of additional factors such as insulin-like growth factor (IGF), fibroblast growth factor (FGF), and transforming growth factor β (TGF β). (C) These factors attract prostate cancer cells, further enhancing their proliferation and growth. ET1 = endothelin 1; PDGF = platelet-derived growth factor; BMP = bone morphogenetic protein; RANK = receptor activator of nuclear factor κ B; RANKL = RANK ligand; OPG = osteoprotegerin.

Several skeletal complications can occur during the progression of bone metastases or because of osteoporosis induced by ADT (or both), including fractures, uncontrolled pain, nerve entrapment, spinal cord compression, and hypercalcemia. Risk factors for ADT-induced osteoporosis, such as pre-existing conditions (age, family history, Asian or Hispanic heritage, smoking, cortisone use), pre-existing bone loss, and duration of ADT should be addressed early during the evaluation if effective prevention is to be considered⁸.

2.3 Clinical Manifestations and Diagnosis of Skeletal Metastases

The diagnosis of bone complications begins with a thorough history and physical examination. It is

very common to misinterpret bone complications as arthritis or other benign conditions that are frequent in this population. The most common symptom is pain that affects the patient’s daily activities. Careful examination, with application of a moderate amount of pressure on bone sites, can occasionally detect malignant osseous involvement. Blood tests should include calcium and alkaline phosphatase. Two other tests are also being used to diagnose and monitor bone-targeted therapies: urinary N-telopeptide (NTX) and bone-specific alkaline phosphatase⁹. Both tests reflect excessive bone turnover, characteristic of osteoblastic bone metastases from pCa. New markers of bone resorption, such as the enzyme tartrate-resistant acid phosphatase (TRAP) are also available and may be useful.

Ultimately, imaging techniques will confirm the diagnosis. Bone scintigraphy has the best sensitivity in detecting bone involvement in pCa, but because of scintigraphy's lack of specificity, plain radiography, computed tomography, or magnetic resonance imaging are frequently required in equivocal cases. Bone biopsy is the most accurate method for confirming the cause of bone lesions, but it is invasive and usually unnecessary¹⁰. Early diagnosis is imperative, because several available therapeutic options can successfully reduce the morbidity linked to osseous involvement by pCa.

Skeletal complications are frequent in advanced pCa because of the synergistic effect of osseous involvement and the side effects of ADT. Other than influence on quality of life, pathologic fractures can eventually affect overall survival because of multiple complications initiated by the original event. A study published in 2007 analyzed data from pCa patients enrolled in randomized trials of zoledronic acid. Patients who presented pathologic fractures during the trial had a more than 20% increased risk of death¹¹. A recent retrospective study on patients with castrate-resistant pCa demonstrated reduced overall survival when patients presented bone pain [hazard ratio (HR): 2.1; $p = 0.007$] or higher scores on bone disease extension (HR: 1.7; $p = 0.033$)¹².

Because the effect on quality of life and survival was well demonstrated, it is critical to determine when and how to treat bone metastases. The advent of hormone resistance is a major risk factor, and skeletal complications are unusual in hormone-sensitive patients. Otherwise, extension of bone disease and bone pain are the best predictors of occurrence of bone complications¹³.

2.4 Targeting Bone Metastases

2.4.1 Bisphosphonates

Bisphosphonates are stable analogues of pyrophosphate and represent a class of drugs that prevent bone loss by inhibiting osteoclast-mediated bone resorption. They are the drugs most widely used to target bone metastases. In receiving bisphosphonates, patients with established bone metastases obtain significant benefit in the prevention of severe skeletal complications, including pain, nerve compression, and fractures^{14,15}. Bisphosphonates approved by the U.S. Food and Drug Administration for the treatment of cancer-related skeletal complications include zoledronic acid, alendronate, clodronate, and pamidronate.

The most potent drug in this class and the first approved in the pCa setting is zoledronic acid. Two trials initially demonstrated the benefits of zoledronic acid in bone metastases from breast cancer, multiple myeloma, and lung cancer^{16,17}. Subsequently, a large randomized clinical trial situated this drug as a potential standard of care in patients at risk of bone

complications from advanced pCa¹⁸. That double-blind controlled trial randomized castrate-refractory patients with established bone metastases to intravenous zoledronic acid 4 mg or 8 mg or to placebo every 3 weeks. A higher incidence of renal failure occurred in the 8-mg group, and the dose for that arm was reduced to 4 mg. As compared with the placebo group, the group receiving zoledronic acid had an 11% absolute reduction and a 25% relative reduction in skeletal-related events ($p = 0.02$). The median time to first skeletal event was also significantly extended to 488 days from 321 days ($p = 0.009$). Furthermore, the clinical benefits were maintained even with longer-term treatment (24 months).

Similar results were not observed with other bisphosphonates (clodronate and pamidronate; see Table 1). A randomized trial by the National Cancer Institute of Canada of intravenous clodronate (1500 mg every 3 weeks) demonstrated no clinical benefit for men with bone metastases receiving the drug as compared with those receiving placebo. Both arms received mitoxantrone and prednisone as baseline treatment. One limitation of this trial was the fact that 77% of subjects had mild pain, and perhaps the number of events was insufficient to reach significance¹⁹. Laboratory data from pamidronate trials (INT05 and Protocol 032) support the theory that the osteoclast inhibition achieved with this drug is not as intense as that seen with zoledronic acid (the reduction in urinary NTX levels is less significant)²⁰.

Clodronate was also tested in patients with bone metastases still sensitive to ADT, a generally infrequent clinical scenario. A double-blind controlled trial randomized 311 men to oral clodronate or to placebo for 3 years. Initial follow-up at 5 years failed to demonstrate any benefit in overall survival or progression of symptomatic bone disease²¹; however, a recent update revealed a significant overall survival benefit at 8 years (22% vs. 14%)²².

The idea of using bisphosphonates to prevent skeletal complications in early castrate-naïve metastatic disease is very attractive. Although such treatment is indicated in other cancers, no available data currently support the use of bisphosphonates at the time of bone metastases in pCa patients not yet failing castration. A current trial (Cancer and Leukemia Group B/Cancer Trials Support Unit 90202) was designed to answer that question. Approximately 680 patients are being randomized to receive zoledronic acid in association with ADT as soon as bone metastases are detected or when castrate-resistant disease develops. Unfortunately, the oral bioavailability of bisphosphonates is relatively poor, and the parenteral route is favoured. Although quite rare, significant side effects, including renal dysfunction and osteonecrosis of the jaw can occur^{23,24}.

Ibandronate is another drug that showed good results in breast cancer and has also been evaluated as an alternative in pCa. It has the advantage of oral

TABLE 1 Most relevant trials of bisphosphonates on preventing skeletal complications in advanced prostate cancer

Reference	Study short name	Population	Pts (n)	Drug	Outcomes
Ernst <i>et al.</i> , 2003 ¹⁹	NCIC PR06	Castration resistant, symptomatic	209	Mitoxantrone and prednisone, with or without 1500 mg IV clodronate every 3 weeks until progression	No significant difference in palliative response, symptomatic disease, progression-free survival, overall survival, or quality of life
Small <i>et al.</i> , 2003 ²⁰	032/INT05	Castration resistant, symptomatic	378	Pamidronate 90 mg IV vs. placebo every 3 weeks for 27 weeks	Number of bone complications equal in pamidronate and placebo arms ($p=1.0$); no significant difference in pain or analgesic use
Saad <i>et al.</i> , 2004 ¹⁸	039	Castration resistant, asymptomatic or minimally symptomatic	643	Zoledronic acid 4 mg or 8 mg vs. placebo every 3 weeks for 15 months	Significant reduction (25%) in proportion of patients experiencing at least 1 bone complication ($p = 0.021$); time for first skeletal event extended; trend toward improved survival
Dearnaley <i>et al.</i> , 2009 ^{21,22}	MRC PR05	Castration-sensitive	311	Clodronate 2080 mg oral vs. placebo for 3 years	Reduction in number of skeletal-related events not significant (49% vs. 41% placebo); follow-up revealed an overall survival benefit (hazard ratio: 0.77; $p = 0.03$)

Pts = patients; NCIC = National Cancer Institute of Canada; IV = intravenous; MRC = U.K. Medical Research Council.

administration. Results from two nonrandomized trials demonstrated pain reduction for more than 80% of patients receiving ibandronate^{25,26}. Only one randomized trial was conducted investigating ibandronate in breast, myeloma, and pCa. The results focused on laboratory tests, and a significant reduction in calcium excretion and biochemical markers of bone resorption was reported ($p < 0.002$). Given that only 16 pCa patients were enrolled, the clinical relevance of these results for pCa remains limited²⁷. Therefore, in the prevention of bone complications, zoledronic acid is the recommended treatment for patients with castrate-resistant pCa and bone metastases. Duration of treatment is still under debate, but longer-term therapy appears to remain effective.

2.4.2 Denosumab

An important step in the progression of bone metastases is the secretion of growth factors by tumour cells, inducing stromal cells and osteoblasts to secrete RANKL, an essential mediator of osteoclast formation, function, and survival. Denosumab is a fully human monoclonal antibody that has RANKL as its specific target. Denosumab was initially used to treat non-cancer-related osteoporosis in postmenopausal women and was shown to prevent fractures²⁸. The rationale for denosumab in pCa is based on the concept that bone metastases from pCa demonstrate intense bone resorption despite a typically dense and sclerotic appearance. A randomized phase II open-label trial reported the effects of denosumab on bone turnover markers and skeletal events in patients with bone metastases and increased NTX despite previous treatment with zoledronic acid²⁹. A subset analysis of the 50 pCa patients enrolled showed that those treated with denosumab had a greater reduction in NTX levels (32%

vs. 84%) and fewer skeletal complications (3% vs. 19%)³⁰. Overall toxicity appeared to be very low, and because the drug can be delivered subcutaneously, it promises to be convenient.

The definitive role of denosumab in pCa treatment is still under investigation. Two important trials investigating clinical benefits of denosumab are currently ongoing and will include more than 3000 patients. Protocol 103 was designed to evaluate denosumab against zoledronic acid in the prevention of skeletal complications from pCa bone metastases. Protocol 147 is randomizing castrate-resistant patients with no bone metastases to denosumab or to placebo and will assess the potential benefit of denosumab in preventing initial skeletal involvement¹⁵.

2.4.3 Bone-Seeking Radiopharmaceuticals

The bone-seeking radiopharmaceuticals were created based on the rationale that targeted radiation delivered by bone-seeking particles could enhance activity in bone metastases, sparing healthy tissue. A combination of radionuclides (sodium-³²P-phosphate, ⁸⁹Sr-chloride, ¹⁵³Sm-lexidronam, ¹⁸⁶Re-HEDP), pain medication, and bisphosphonates is a potential form of treatment for pCa patients³¹, potentially allowing for simultaneous treatment of multiple sites and occult disease. A recent phase II trial addressed the benefit of radionuclides associated with standard chemotherapy in pCa³². Unfortunately, almost all studies involving these drugs recruited a small number of patients and had subjective endpoints with no standardized measurements.

2.5 The Role of Radiation

Radiotherapy has long been used in the treatment of symptomatic bone metastases with excellent results.

Even when there is no effect on survival, the benefits of radiation for reducing pain, fractures, and spinal cord compression are clear. However, the ideal time at which to irradiate sites of metastases that are prone to complications is still debated. For example, some suggest that prophylactic radiotherapy should be applied to axial metastases or at the hips as soon as minimal pain is present or even when asymptomatic lesions felt to be at risk of future fracture are discovered³³. A detailed evaluation of bone-disease progression and an individual assessment of fracture risk is important to reduce skeletal events overall. The optimal dose–fractionation schemes remain unclear. It appears that low single doses (6 ± 15 Gy) are equivalent to multiple fractions delivering higher doses (20 ± 40 Gy)³⁴.

2.6 Chemotherapy

With the reporting of two phase III trials demonstrating a modest overall survival benefit, docetaxel-based chemotherapy became the recommended treatment when symptomatic castrate-resistant disease developed. Those studies also showed significant palliative improvement in pain related to bone disease. Nevertheless, most patients will experience progression within 6 months after first-line chemotherapy³⁵. Although pain reduction is achieved with systemic chemotherapy, it remains unclear if skeletal complications are improved³⁶. Therefore, in patients with symptomatic castrate-resistant PCA, the recommended approach includes docetaxel and prednisone chemotherapy in association with zoledronic acid.

2.7 Drug Development

Because of its prevalence, bone metastasis from PCA is the focus of intense research around the world. As the molecular mechanisms of cancer metastasis are elucidated, new targeted therapies are being developed for clinical assessment. Several targets have the potential to impair tumour growth and perhaps the natural history of bone metastases.

Atrasentan, a potent selective endothelin A receptor antagonist, was tested against placebo. Despite effects on biologic markers, no significant clinical benefit could be demonstrated³⁷. A new trial [Southwest Oncology Group (swog) 0421] is attempting to determine if atrasentan has benefit when combined with standard chemotherapy. Other endothelin A receptor antagonists such as ZD4054 are also showing promise and are being actively tested in clinical trials³⁸.

A recent phase II trial testing cilengitide (an integrin competitive inhibitor) was recently reported³⁹. The drug did not meet the protocol aims, but some clinical and biologic results warrant further investigation.

Another exciting drug class with potential effect on skeletal metastases is the Src kinase inhibitors. The Src family kinases (SFKs) are involved in almost

all processes during PCA progression and metastasis. In addition, Src overexpression was demonstrated in castrate-resistant PCA. Two novel drugs targeting SFK (dasatinib and saracatinib) are being tested for their potential to inhibit prostate tumour growth and metastasis and also osteoclast activity and bone resorption. Phase II trials have demonstrated good safety profiles and interesting measurable responses in bone metastases. Currently, phase III trials combining these agents with docetaxel are being conducted.

2.8 Prevention of ADT-Related Bone Complications

Men receiving long-term ADT are not only at risk of serious complications from osseous metastases—their whole bone integrity is at risk. Thus, in patients with PCA affecting bone, two principal synergistic mechanisms lead to bone complications: cancer erosion and declining bone integrity because of castration.

Several changes in lifestyle have the potential to reduce the progression of osteoporosis and prevent complications of bone metastases. Smoking cessation, moderate caffeine and alcohol intake, and regular weight-bearing exercise, if permitted, are advocated. Simple measures to prevent falls, such as adapting the furniture at home and avoiding rugs, should be considered⁴⁰. More importantly, calcium and vitamin D supplementation should be instituted at the initiation of ADT⁴¹.

Bisphosphonate trials (zoledronic acid, alendronate, pamidronate, neridronate) in the nonmetastatic PCA setting have failed to show benefit in preventing fractures despite a clear and strong benefit in bone mineral density (BMD)^{42–46}. It is possible that the reduction in fracture risk benefits only those patients with certain risk-factor phenotypes. These multiple factors are being addressed in a recently developed fracture risk assessment model⁴⁷. Furthermore, selective estrogen receptor modulators (raloxifene and toremifene, for instance) operate using the same pathway, binding to estrogen receptors on osteoblasts and osteoclasts. The addition of raloxifene or toremifene to ADT showed clear benefits in improved BMD for patients taking both agents^{48–50}. More importantly, a recent trial of denosumab in the setting of nonmetastatic PCA demonstrated a statistically significant reduction of 62% in the 3-year incidence of new vertebral fractures⁵¹.

3. SUMMARY

Preventing bone complications in patients with advanced PCA is still challenging. Although no therapeutic modality has shown significant improvement in overall survival, several new treatments have shown clinically significant palliative improvements and prevention of serious bone complications. Although all patients with advanced PCA are clearly at risk of skeletal complications, reliable tools to quantify this risk

and to properly select patients for early, aggressive bone-targeted therapy are lacking. Physicians must recognize the possibility of complications, evaluate and quantify the risk, follow disease progression carefully, and individually apply one or more available modalities to improve outcomes. Clinicians must be vigilant in the early investigation of bone metastases so as to institute an effective program for skeletal health in the pCa patient.

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