The role of bisphosphonates in the management of bone metastases in prostate cancer

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Bone metastases are associated with significant skeletal-related morbidity that negatively correlates with quality of life and survival in patients with prostate cancer. Once prostate cancer has metastasized to bone, the median survival of patients is approximately 30 to 53 months; therefore, the chronic consequences of bone complications must be taken into consideration when developing long-term therapeutic strategies in this patient population. In addition to the bone-damaging effects of metastases, bone loss related to long-term hormonal therapy, as well as age-related bone loss, further compromise bone integrity in patients with advanced prostate cancer. This article reviews the burden of skeletal complications in patients with prostate cancer, and the evidence for the use of bisphosphonates for the treatment of skeletal morbidity in this patient population.

Key Words: bisphosphonates, bone metastases, prostate cancer

Introduction

In 2003, an estimated 18800 Canadian men were diagnosed with prostate cancer, and 4200 men died from the disease.[1] It is estimated that 85% to 100% of men who die from prostate cancer have bone metastases.[2] Bone metastases are associated with significant skeletal-related morbidity that negatively correlates with quality of life and survival in patients with prostate cancer.[3-6] Once prostate cancer has metastasized to bone, the median survival of patients is approximately 30 to 53 months.[7] Thus, the chronic consequences of bone complications must be taken into consideration when developing long-term therapeutic strategies in this patient population.

In addition to the bone-damaging effects of metastases, bone loss related to long-term hormonal therapy, as well as age-related bone loss, further compromise bone integrity in patients with advanced prostate cancer.[2,8-10]

The purpose of this article is to review the burden of skeletal complications in patients with prostate cancer, and to review the evidence for the use of bisphosphonates for the treatment of skeletal morbidity in these patients. A literature search of MEDLINE was performed to identify relevant articles, such as relevant reviews, observational studies (cohort or case-control), clinical trials, systematic reviews, and meta-analyses. Search terms included, but were not limited to: 'prostate cancer', 'bone metastases',

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'skeletal/bone complications', 'bone mineral density', 'bone loss', 'skeletal-related events', and 'bisphosphonates'. The bibliographies of relevant articles were searched, as well as the abstracts of scientific meetings.

Natural history of skeletal-related morbidity in patients with prostate cancer

Bone is the favored site of metastatic prostate cancer. Patients with bone metastases secondary to prostate cancer include those whose disease has progressed despite curative treatment, those who presented with metastatic prostate cancer and painful bone metastases at initial diagnosis, and those who presented with a high prostate-specific antigen (PSA) level with no symptoms and were found incidentally to have asymptomatic bone metastases. In the ongoing CaPSURE study, 2.6% of patients with newly diagnosed prostate cancer were found to harbor bone metastases, and earlier published studies have reported estimates as high as 10% to 20%.[11]

Symptomatic bone metastasis is associated with debilitating pain that can be difficult to manage with analgesics alone and requires palliative radiation treatment.[12] The focal and generalized bone destruction caused by bone metastasis increases the risk for skeletal-related events (SREs), including pathologic bone fractures and spinal cord compression.[7] A recent study found that patients with hormone-refractory metastatic prostate cancer experienced an average of 1.5 morbid SREs each year, with nearly one-third of patients requiring palliative radiotherapy for bone pain.[13] Spinal cord compression is estimated to occur in 7% of all patients with malignant bone disease secondary to prostate cancer and requires immediate intervention to avoid devastating neurologic sequelae, including paraplegia.[14] The severity of cancer-related bone complications is underscored by the fact that the majority of these fractures never heal, and function can often only be restored through orthopedic surgery, which can be associated with significant post-operative morbidity and mortality.[15]

The etiology of prostate cancer-related bone complications is multifaceted, and can arise from factors unrelated to metastases. All men with prostate cancer, including those whose disease has not yet metastasized to bone, have an increased risk for bone complications.[16] Compared with men without prostate cancer, men with untreated prostate cancer have low bone mineral density (BMD), although the underlying reason for this correlation is not yet understood.[17,18] Low BMD is associated with a higher risk of fracture, and predisposes this patient population to skeletal complications.[19-21]

In addition, treatments used for prostate cancer can have deleterious effects on skeletal-related morbidity. Studies have shown that men with prostate cancer experience a yearly 3% to 5% decrease in BMD in the first few years of androgen-deprivation therapy (ADT),[22,23] as well as an increase in the incidence of skeletal fractures.[24] Melton and colleagues followed 429 men who had undergone bilateral orchiectomy for prostate cancer and found that these men were at a 3.4-fold increased risk of fracture compared with the expected rates in the community.[24] Moreover, it has been observed that skeletal fractures in patients with prostate cancer on chronic ADT negatively correlate with overall survival.[5]

In recent years, the clinical presentation of prostate cancer has shifted significantly, resulting in a dramatic change in the pattern of care. With the widespread use of PSA testing, patients are now being treated with curative intent earlier in the disease course, being diagnosed with relapse earlier, and subsequently being treated earlier with ADT. Thus, patients whose disease continues to progress despite curative treatment with ADT have been on long-term ADT before their disease metastasizes to bone and have an even greater risk for skeletal complications.[24]

Bone metastases: pathogenesis, workup, and treatment

The underlying pathogenesis of bone complications from metastatic disease appears to result from abnormal bone remodelling.[26] Bone lesions in patients with bone metastases appear to be primarily osteoblastic on radiograph; however, an increase in osteoclastic activity appears to contribute substantially to both disease- and treatment-related bone complications.[26]

The high rate of malignant skeletal morbidity in patients with prostate cancer highlights the importance of identifying bone metastases in these patients. Bone scans are the most commonly used method for the detection of bone metastases in prostate cancer, and are essential in the evaluation of symptomatic patients.[27]

At this time, there is no Canadian consensus regarding the use of bone scans in the clinical work-up of patients with prostate cancer. A number of guidelines recommend that a bone scan be performed at diagnosis in patients who meet a number of

TABLE 1. **National Comprehensive Cancer Network criteria for the use of bonse scans in newly diagnosed patients with prostate cancer[28]***

T1-T2 + PSA >10 ng/mL, OR
Gleason ≥8, OR
T3-T4, OR
Symptomatic

*One or more criteria

PSA = Prostate-specific antigen

specified criteria Table 1.[28,29] Bone scans are also recommended during follow-up for any patient who becomes symptomatic. For asymptomatic patients with hormone-refractory disease, the absolute PSA level[30] and the rate of a rising PSA may be helpful to identify patients who are harboring clinically detectable metastases and at risk of more rapid disease progression.[31]

There are currently no Canadian guidelines for the treatment of bone metastases in men with prostate cancer. The treatment strategy used will be dictated by whether the patient has hormone-sensitive or hormone-refractory disease, as well as whether the patient is symptomatic or asymptomatic.[32] Treatment is palliative and can include radiotherapy (i.e., external beam radiation, radiopharmaceuticals), hormonal therapy, orthopedic interventions, chemotherapy, narcotics and, most recently, bisphosphonates to control the pain and reduce the risk for subsequent skeletal complications.

Rationale for the use of bisphosphonates

Bisphosphonates are nonhydrolizable synthetic analogues of pyrophosphate, a normal constituent of the bone matrix. Bisphosphonates are effective inhibitors of osteoclast-mediated bone resorption. They preferentially adhere to active sites of bone remodelling, where, following osteoclast ingestion, they interfere with key cellular regulatory pathways within the osteoclast.[33,34]

Studies of bisphosphonates in breast cancer and multiple myeloma—malignancies characterized by osteolytic metastases—have shown that they are effective in reducing skeletal complications, and may result in an up to 40% relative risk reduction for developing a SRE.[35-38] Results of a recent phase III randomized, controlled trial have also demonstrated efficacy for bisphosphonates in the treatment of skeletal metastases in patients with other solid tumors, including lung cancer.[39] A recent systematic review, that assessed the evidence for the role of bisphosphonates in the reduction of skeletal morbidity in cancer patients with metastatic bone disease, found that bisphosphonate therapy was associated with a significant reduction in most skeletal morbidity end points.[22] A recent Cochrane systematic review, which specifically examined the use of bisphosphonates to reduce pain secondary to bone metastases, found evidence to support the use of bisphosphonates in providing some pain relief when analgesics and/or radiotherapy are inadequate.[40]

Prostate cancer bone metastases are characteristically described as osteoblastic bone lesions, since on radiographs they appear as areas of increased bone density, suggesting excessive bone formation by osteoblasts. They should, however, be more accurately described as mixed osteoblastic/osteolytic lesions, since both osteoblastic and osteoclastic activity appear to be implicated in metastatic osteoblastic bone disease.[26] Evidence that bone resorption is increased in osteoblastic metastases comes from both histological and biochemical studies.[41-44]

Pharmacokinetics and pharmacodynamics of bisphosphonates

Members of the first generation of bisphosphonates, including clodronate and etidronate, are relatively weak inhibitors of bone resorption. The second-generation bisphosphonate pamidronate is approximately 20 times more potent than clodronate. Zoledronic acid, a third-generation bisphosphonate, is the most potent of the currently available bisphosphonates and is approximately 100 times more potent than pamidronate.[45]

Although all bisphosphonates can be administered either intravenously or orally, the bioavailability of oral bisphosphonates is extremely low.[46] Generally, only a small percentage of an oral dose is absorbed from the gastrointestinal tract, and intake of food or beverage further diminishes absorption to negligible levels. Increasing the oral dose of the bisphosphonate to boost the bioavailability has not been well tolerated, and has been associated with an increase in gastrointestinal side effects.[46] Intravenous (IV) bisphosphonates have better bioavailability than oral bisphosphonates,[47,48] and pooled results of trials that used IV bisphosphonates to treat skeletal complications were highly significant compared with results of trials that used oral bisphosphonates.[22]

Bisphosphonates are generally well tolerated, but

toxicity may vary considerably from one compound to another.[46] These compounds are not metabolized and are cleared renally, and may result in elevated serum creatinine levels. Renal impairment appears to be related to dose and the rate of infusion, and to the specific bisphosphonate being administered.[46]

Bisphosphonates in prostate cancer

Early clinical trials examined oral and IV clodronate and etidronate in men with symptomatic, analgesic-requiring bone metastases secondary to prostate cancer.[49-51] Although some nonsignificant effects on outcomes related to bone pain were observed, none of these studies provided compelling evidence for IV clodronate and etidronate use in symptomatic prostate cancer. However, these studies were small, underpowered to detect differences in outcomes, and used bisphosphonates that were relatively low in potency compared with the newer bisphosphonates.

Oral clodronate, IV clodronate, IV pamidronate, and IV zoledronic acid have all been studied in more recent phase III randomized trials Table 2.[13,50-55] Three hundred eleven patients who were started on or were responding to first-line hormone therapy for bone metastases were treated with oral clodronate or placebo for a maximum of three years.[56] After a median follow-up of 59 months, patients treated with clodronate showed nonsignificant differences in symptomatic bone progression-free survival times and

TABLE 2. **Efficacy of bisphosphonates in randomized, placebo-controlled trials in patients with bone metastases secondary to prostate cancer**

Study	Patients (n)	Drug	Dose	Efficacy results
Smith, 1989[51]	57	Etidronate	7.5 mg/kg (IV, days 1–3), then 400 mg/day (oral)	No significant benefits
Elomaa et al., 1992[50]	75	Clodronate	3200 mg/day (first month), then 1600 mg/day (oral)	Decreased pain and analgesic use (first month only) Decreased serum calcium levels
Kylmala et al., 1997[52]	57	Clodronate	300 mg/day (IV, days 1–5), then 1600 mg/day (oral)	Decreased pain by 10% (nonsignificant)
Strang et al., 1997[53]	55	Clodronate	300 mg/day (IV, days 1–3), then 3200 mg/day (oral)	No significant benefits
Ernst et al., 2003[54]	208	Clodronate	1500 mg (IV) q 3 weeks	Decreased pain (nonsignificant)
Small et al., 2003[55]	236	Pamidronate	90 mg (IV) q 3 weeks	No significant benefits in pain or proportion of patients with SREs
Saad et al., 2004[13]	643	Zoledronic acid	4 mg (IV) q 3 weeks	Decreased proportion of patients with ≥1 SRE (p=0.021) Increased time to first SRE (p=0.011) Decreased rate of skeletal morbidity (p=0.006)

IV = Intravenous; SRE = Skeletal-related event

overall survival compared with patients treated with placebo. Patients in the clodronate group were also significantly less likely to have a worsened World Health Organization (WHO) performance status. However, patients in the clodronate group had a significantly higher incidence of any of the adverse events reported, including gastrointestinal problems. Results of subgroup analysis suggested that clodronate might be more effective the sooner it is administered after diagnosis of metastatic bone disease.[56]

In a randomized, double-blind, controlled trial, 209 patients with bone metastases secondary to advanced prostate cancer were randomly assigned to receive either IV clodronate or placebo, added to their mitoxantrone/prednisone regimen.[54] In these patients, the addition of clodronate did not significantly increase the rate of palliative response compared with placebo. The median duration of response, symptomatic disease progression-free survival, overall survival, and overall quality of life were also similar between the two groups. Thus, results from this study suggest that clodronate cannot be recommended as a standard treatment for palliation of symptomatic bone disease in this patient population.

The effect of IV pamidronate on bone pain control in metastatic prostate cancer patients was evaluated in two multicenter, double-blind randomized controlled trials.[55] The primary objective was to determine whether pain or analgesic use was reduced in association with palmidronate use. When the results of the two trials were pooled, there were no sustained significant differences between the pamidronate and placebo groups in self-reported pain measurements or analgesic use. The proportion of patients with a SRE was also similar between the two groups Figure 1. Thus, IV pamidronate failed to demonstrate an overall treatment benefit compared with placebo in the overall patient population at study end.

In a large randomized controlled clinical trial evaluating the efficacy of zoledronic acid, 641 patients with hormone-refractory advanced prostate cancer and documented bone metastases were randomly assigned to receive placebo, 4 mg, or 8 mg of IV zoledronic acid.[13] Patient characteristics were similar between the three treatment groups, with more than 90% of the patients in each group having an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; few had metastatic disease at sites other than bone and/or lymph nodes, and more than 90% of the patients were older than 60 years. During the study, the 8 mg dose was dropped to 4 mg as it was associated with a rise in serum creatinine levels

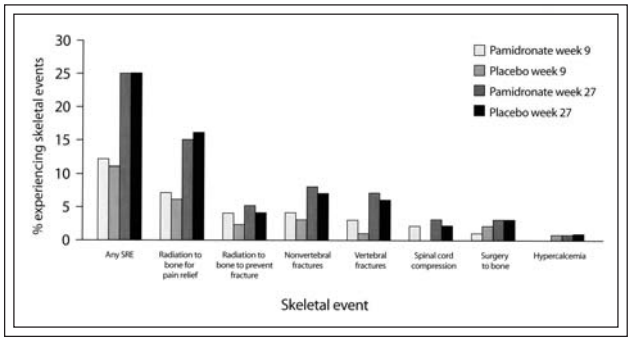

Figure 1. Skeletal-related events (SREs) – pamidronate versus placebo.[55]

in some patients; subsequently, the 8/4 mg group was not included in the efficacy analysis. Additionally, to address this observation, the infusion time was increased to 15 minutes. The primary efficacy end point was the proportion of patients having at least one SRE, which was prospectively defined as pathological fractures, spinal cord compression, bone surgery, bone radiation therapy, and change of antineoplastic therapy to treat bone pain. Secondary end points included time to first SRE, time to overall disease progression, pain relief, bone biochemical markers, and quality of life.

In the 4 mg zoledronic acid group, the proportion of patients who had a SRE over the 24-month study period was significantly lower compared with the placebo group (38% vs 49%; p=0.029). Multiple event analysis showed that zoledronic acid reduced the risk of developing SREs by 36% (hazard ratio: 0.64; p=0.002) Figure 2.[12] Zoledronic acid also prolonged the time to the first skeletal complication by more than

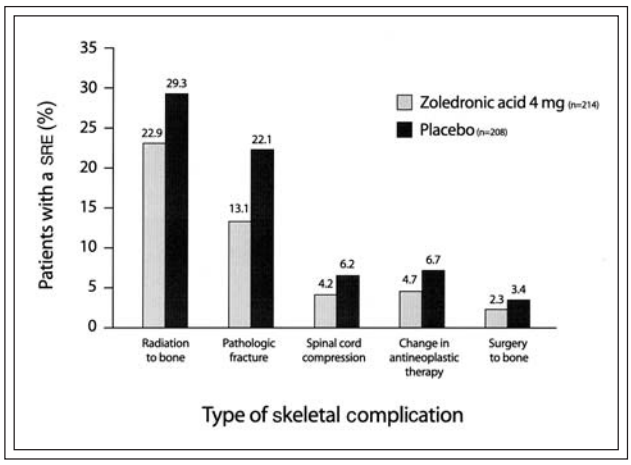

Figure 2. Reduction in skeletal-related events (SREs) with zoledronic acid in men with hormone-refractory prostate cancer refractory to bone.[13]

five months compared with placebo. Furthermore, the mean skeletal morbidity rate for all SREs combined was significantly lower in the 4 mg zoledronic acid group (0.77 vs 1.47; p=0.005).[13] Even though the study used a composite end point of a combination of SREs, the risk of experiencing each individual type of SRE was also lower for patients who received zoledronic acid. The risk of experiencing a pathologic fracture was significantly reduced in patients in the zoledronic arm.[13] Overall, disease progression, survival, and quality of life scores were similar between the two groups. Flu-like symptoms (e.g., mild-to-moderate fatigue, fever, and myalgia) occurred more frequently in the zoledronic acid group. The results of this trial are the first to demonstrate a significant benefit in terms of SREs for a bisphosphonate in the treatment of patients with bone metastases secondary to prostate cancer. This is potentially a key finding, given that in this patient population SREs are associated with reduced physical, functional, and emotional well-being.[6]

Although bone metastases in prostate cancer appear osteoblastic on radiographs, the pathology is more complex than radiographic appearance suggests. It is now clear that bone resorption by osteoclastic activity is also a key mechanism underlying metastatic bone disease in prostate cancer. This recent large, randomized trial has shown that zoledronic acid is able to significantly reduce the skeletal morbidity of metastatic bone disease in advanced prostate cancer. The role of bisphosphonates in the treatment of bone metastases secondary to advanced prostate cancer is continuing to evolve, and ongoing studies evaluating the use of zoledronic acid during earlier stages of the disease is a rational next step.

Clinical use of bisphosphonates

For patients with prostate cancer, complications resulting from bone metastases carry significant morbidity for this population. The data presented above suggests that treatment with zoledronic acid aids in reducing skeletal events associated with skeletal metastases secondary to advanced hormone-refractory prostate cancer. Thus, in these patients, a measured approach to treatment with zoledronic acid is warranted after careful consideration of the potential benefit of reducing the chance of symptomatic and asymptomatic skeletal-related events against the potential side effects and difficulties associated with therapy. Ongoing studies will assess the impact of the use of bisphosphonates on progression and the complications of treatment-induced osteopenia in patients with earlier stages of prostate cancer. □

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