# Bone-targeted therapy in prostate cancer

*Fred Saad* *

*University of Montreal Hospital Center, Montreal, Quebec, Canada*

## 1. Introduction

Androgen deprivation therapy (ADT) is standard for advanced prostate cancer and is now increasingly used as adjunct therapy in high-risk or locally advanced disease and for the treatment of recurring disease based on rising prostate-specific antigen levels. Testosterone stimulates bone formation directly by stimulating the osteoblast proliferation, inhibiting the apoptosis of both osteoblasts and osteoclasts, and indirectly by being a precursor of oestrogen which is also involved in inhibiting osteoclastic function (bone resorption). The effects of testosterone on preserving bone health are lost in the hypogonadal state induced by ADT [1]. The impact of ADT on bone loss and osteoporosis is well established through multiple studies. In one of these studies, non-metastatic prostate cancer cases were followed for 10 years; none of the patients on ADT had normal bone mass density (BMD) at the end of the study, and the prevalence of osteoporosis ($T$ score $< -2.5$) was approximately 50% by 4 years and 80% by 10 years in men on ADT [2].

Bone metastases will occur in over 90% of men with lethal castration-resistant prostate cancer (CRPC). Due to the combined effect of bone fragility due to ADT and the presence of bone metastases, almost all patients will experience some form of morbidity related to bone metastases prior to succumbing from the disease. Complications go beyond pain and include pathological fracture, the need for palliative radiation or surgery, and spinal cord compression. These events impair quality of life and place a significant burden on health-care resources.

## 2. Management options

### 2.1. *Life style modification and supplementation*

Regular exercise, smoking cessation, lowering alcohol and caffeine intake, as well as oral vitamin D (800 IU daily) and calcium (500–1500 mg daily) supplementation are helpful in attenuating ADT-related bone loss, but they are insufficient to prevent or treat ADT-induced bone loss [3].

### 2.2. *Bone targeted therapy (anti-resorptive agents)*

Bisphosphonates are the first and most widely used of the anti-resorptive agents. Due to their structural similarity to pyrophosphate, a normal component of bone matrix, they are integrated in the bone matrix by binding to hydroxyapatite crystals, resulting in inhibition of osteoclast-mediated bone resorption. Non-nitrogen-containing bisphosphonates are metabolized by osteoclasts to cytotoxic compounds, while nitrogen-containing bisphosphonates exert their effects on osteoclasts and tumour cells by inhibiting a key enzyme in the mevalonate pathway and by inducting osteoclast apoptosis. Nitrogen-containing bisphosphonates (e.g., pamidronate, zoledronic acid) are more potent than non-nitrogen-containing bisphosphonates (e.g., clodronate). Zoledronic acid is unique in that it contains two nitrogen groups, and it has been shown to be 40–850-fold more potent than other bisphosphonates [4].

In the setting of non-metastatic prostate cancer, bisphosphonates have consistently been found to reduce BMD loss associated with ADT in multiple randomized controlled trials, but none have had sufficient power or duration to demonstrate a reduction in fractures [5].

Zoledronic acid is the only bisphosphonate and the first osteoclast-targeted agent that has shown a protective effect against skeletal-related events (SRE) in patients with metastatic castration-resistant prostate cancer. The phase 3 study showed a 48% reduction in the mean annual incidence of SRE ($P = 0.005$), 5 months prolongation in the median time to first SRE ($P = 0.009$) and 36% reduction in the ongoing risk of SREs at 24 months [6,7].

Bisphosphonate-induced nephrotoxicity is a major concern, especially with intravenous bisphosphonates. Renal function monitoring and dose adjustment according to creatinine clearance are crucial to prevent significant deterioration in renal function. Other side effects include self-limiting flu-like symptoms occurring with the first infusions, hypocalcaemia and osteonecrosis of the jaw (ONJ) [8].

The zoledronic acid bone metastases prevention study recently reported their results. The Zometa European Study [ZEUS] reported that there was no difference in the

* *Corresponding author:* Tel.: +1 514 890 8000x27466.
E-mail address: fredsaad@videotron.ca.
1359-6349/$ - see front matter 
http://dx.doi.org/10.1016/j.ejcsup.2013.07.038

metastases rate after 4 years in high-risk non-metastatic prostate cancer. Of note, the incidence of new metastases was very low at approximately 13% [9].

*Denosumab* is a receptor activator of nuclear factor kappa B (RANK), a member of the tumour necrosis factor (TNF) receptor superfamily expressed by osteoclast precursors, and its ligand (RANKL) plays an essential role in regulating the osteoclast life cycle at different levels. Binding of the RANKL, secreted by osteoblasts and bone-marrow stromal cells, to its receptor RANK leads to differentiation, activation, and survival of osteoclasts which induce bone resorption [10].

Denosumab is a fully human monoclonal antibody that specifically targets RANKL, thus effectively inhibiting osteoclastic function and bone resorption, In a randomised placebo-controlled study in patients with non-metastatic prostate cancer receiving ADT, denosumab (60 mg subcutaneously every 6 months) was associated with significant improvements in BMD at the lumbar spine (6.7%), the total hip (4.8%) and distal one third of the radius (5.5%). Denosumab was also the first agent to show a reduction in the incidence of new vertebral fractures (1.5% versus 3.9%; $P = 0.006$) in patients on ADT [11].

In the setting of metastatic CRPC, denosumab (120 mg subcutaneously every 4 weeks) compared to zoledronic acid (4 mg intravenously every 4 weeks) significantly improved the time to first SRE (20.7 versus 17.1 months; $P < 0.001$ for non-inferiority; $P = 0.008$ for superiority). Overall survival and progression-free survival were similar for both drugs. Hypocalcaemia was more common with denosumab (13%) than with zoledronic acid (6%) ($P < 0.0001$) and a non-significant trend towards higher osteonecrosis of the jaw was seen with denosumab (2.3% versus 1.3%; $P = 0.09$) [12]. Calcium and vitamin D supplementation and monitoring of calcium levels while on therapy are essential to reduce the risk of hypocalcemia.

In another placebo-controlled trial in non-metastatic CRPC, denosumab (120 q monthly) significantly increased the bone-metastasis-free survival in patients with non-metastatic CRPC by a median of 4.2 months (29.5 versus 25.2 months; HR, 0.85; 95%CI, 0.73–0.98; $P = 0.028$) [17]. Although hypocalcaemia was much lower in the setting of non-metastatic CRPC, the risk of ONJ was higher given the longer exposure time to denosumab [13].

### 2.3. *Osteonecrosis of the jaw (ONJ)*

Osteonecrosis of the jaw is defined as exposed necrotic bone in the maxillofacial region that persists for more than 8 weeks. The incidence of ONJ in patients with CRPC receiving denosumab was similar to that in patients receiving zoledronic acid [12]. Although the aetiology is unclear, duration of therapy, poor dental hygiene, invasive dental surgery or ill-fitting dentures, concomitant corticosteroid use, radiotherapy and chemotherapy are identified risk factors. A conservative approach to the management of ONJ is recommended and includes oral rinses, antibiotics, pain control and minimal surface bony debridement to reduce sharp or rough bone surfaces. Biopsies are not recommended unless metastasis to the jaw is suspected. Good oral hygiene, baseline dental evaluation for high-risk individuals and avoidance of invasive dental surgery during therapy reduce the risk of ONJ [14–16]. Most of the cases that were reported had had a tooth extraction or some other form of trauma that may have contributed to the development of ONJ. Most cases were treated conservatively, and less than 10% required bone resection. It is estimated that the risk is approximately 1–2% per year of exposure to bone-targeted therapies such as zoledronic acid and denosumab. Although bone-targeted therapy is beneficial, one must consider the risk of ONJ after 2 years of therapy when deciding whether to continue therapy.

### 2.4. *Radiopharmaceuticals – (radium-223)*

In a recently completed phase III study of patients with metastatic CRPC, patients were randomized on a 2:1 basis to either radium-223 (an alpha-emitting bone seeker) or placebo. To be eligible for the study patients had to have bone metastases and to have progressed after chemotherapy or were not eligible to receive chemotherapy. Patients received either radium-223 or placebo every 4 weeks intravenously. Overall survival (OS) was the primary endpoint. Median survival was 14 months for the treated patients as opposed to 11.2 months for those who received a placebo, conferring approximately a 30% improvement in OS (HR = 0.699, $P = 0.0022$). The updated analysis involving 921 patients confirmed the radium-223 survival benefit (median, 14.9 months vs. 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; $P < 0.001$). The study also showed a 5-month delay in time to skeletal-related events. This agent has recently been approved by the FDA and is the first bone-targeted agent to demonstrate a survival advantage.

## 3. Conclusion

Patients with metastatic prostate cancer are at high risk for skeletal complications, including debilitating bone pain often requiring palliative radiation therapy, pathological fractures, and spinal cord compression. These complications impair quality of life and place a significant burden on health-care resources. They are due to the combined effects of bone metastases and ADT-related bone loss. The use of bone-targeted therapy (denosumab and zoledronic acid) has been shown to significantly delay and reduce the risk of these skeletal complications. Studies have also suggested that introduction of these therapies prior to PAIN or SREs may further improve efficacy. Denosumab (60 mg every 6 months) has recently been approved for prevention of bone loss related to ADT. Most recently the radiopharmaceutical, radium-223, was shown to delay skeletal complications and also to improve overall survival in patients ineligible for or having failed chemotherapy. The combination of early bone-targeted therapy followed by radium-223 later in the disease continuum appears to lead to further improvements in the management of bone metastases in CRPC.

## Conflict of interest statement

Consultant and research conducted with Amgen, Bayer, Novartis.

## REFERENCES


[1] Riggs BL, Khosla S, Melton 3rd LJ. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev 2002;23:279–302.

[2] Morote J, Morin JP, Orsola A, et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology 2007;69:500–4.

[3] Brown JP, Josse RG. Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002;167(Suppl. 10):S1–S34.

[4] Green JR. Bisphosphonates: preclinical review. Oncologist 2004;9(Suppl. 4):3–13.

[5] Egerdie B, Saad F. Bone health in the prostate cancer patient receiving androgen deprivation therapy: a review of present and future management options. CUAJ 2010;4:129–35.

[6] Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458–68.

[7] Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004;96:879–82.

[8] Conte P, Guarneri V. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. Oncologist 2004;9(Suppl. 4):28–37.

[9] Wirth M, Tammela T, Huland H, et al. Efficacy and safety of the Zometa European study Abstract EAU; March 2013.

[10] Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature 2003;423:337–42.

[11] Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009;361:745–55.

[12] Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813–22.

[13] Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 2012;379:39–46.

[14] Hoff AO, Toth BB, Altundag K, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 2008;23:826–36.

[15] Ruggiero S, Gralow J, Marx RE, et al. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Practice 2006;2:7–14.

[16] Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 2012;23:1341–7.

[17] Parker C, Nilsson S, Heinrich D. Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer NEJM 2013;369.