Novel bone protective agents in patients with prostate cancer

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Abstract

Prostate cancer is the most commonly diagnosed non-cuta-
neous cancer and the second leading cause of cancer death in
men. The tissue tropism of prostate cancer for bone coupled
with the skeletal-related adverse effects of Androgen Depriva-
tion Therapy has led to heightened awareness of SREs in ca-
stration resistant prostate cancer. In the European Association of
Urology updated 2015 guidelines on the management of ca-
stration resistant prostate cancer the grade of recommendation
is ‘A’ for offering bone protective agents to patients with bone
metastases (denosumab being superior to zoledronic acid).
The results of larger ongoing studies that assess the efficacy,
safety and cost-effectiveness of denosumab are warranted.

Key words
prostate cancer; castration;
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enzalutamide

Citation

n Castration resistant prostate cancer (CRPC) bone metas-
tases are often present posing a substantial health and eco-
nomic burden because they induce skeletal-related events (SREs: Pathological fractures, spinal cord compression, need for radiotherapy or surgery to the bone). Once bone metastases are di-
agnosed, the survival time varies between 12 and 55 months depend-
ing on various prognostications’. Clinically, bone metastases are the primary cause of morbidity and mor-
tality for men with metastatic CRPC, with 80% - 90% of patients eventually
developing metastatic disease.

Recently, the appearance of two or more new bone lesions on bone scan was includ-
ed as an alternative characterization of CRPC in the guidelines of the European Association of Urology (EAU)17. This stresses the importance of bone protective agents for the prevention and management of skeletal-related events (SREs).

For the last two decades only intravenous (IV) bisphosphonate zoledronic acid has demonstrated efficacy in preventing SREs and has been established in the clinical practice. Recently, subcutaneous (SC) use of denosumab (a fully human monoclonal antibody of the IgG2 subtype against receptor
activated nuclear factor kappa - b ligand: RANKL) has gained Food & Drug Administration (FDA) approval for prevention of SREs in patients with bone metastases from solid tumors and for increasing bone mass in patients with non-metastatic PCa under androgen deprivation therapy (ADT). Furthermore, although initial ADT is uniformly effective, nearly all patients will eventually develop CRPC with bone metastases, thus the development of novel bone-targeted agents such as denosumab is more than welcomed.2

Bisphosphonates
Bisphosphonates have been used to inhibit osteoclast-mediated bone resorption in CRPC and have proven to be highly effective in reducing bone pain. 643 patients who had CRPC3 with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every 3 weeks for 15 consecutive months, or placebo. At 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer skeletal-related events (SREs) compared to the placebo group (44% vs 33%, p = 0.021) and fewer pathological fractures (13.1% vs 22.1%, p = 0.015). Furthermore, the time to first SRE was longer in the zoledronic acid group, thus improving QoL.

Patients were initially randomised to 4 or 8 mg of zoledronic acid, but the 8 mg dosage was later modified to 4 mg due to toxicity. The toxicity (e.g., jaw necrosis) of these drugs, especially amino bisphosphonate, must always be kept in mind4, 5. Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as long-term intravenous bisphosphonate administration6. No survival benefit has been seen in any prospective trial with bisphosphonates.

In a survey which included 200 urologists from 12 European countries including 27442 PCa patients bisphosphonates were used to the same extent in hormone-naive and castration-resistant PCa, with bone metastases, although current guidelines recommend their use only in CRPC. 78-80% of board-certified urologists prescribed BPs in both hormone sensitive PCa and CRPC7.

RANK ligand inhibitors
Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor kB ligand), a key mediator of osteoclast formation, function, and survival. Denosumab binds to RANKL and prevents the maturation of osteoclasts, bone resorption and finally breaks the vicious cycle of bone destruction.

It has been developed as two products with different dosing regimens and therapeutic indications8. In the dose of 60 mg SC, twice yearly, it is indicated for the treatment of bone loss associated with androgen deprivation therapy (ADT) in men with prostate cancer at high risk of fracture. In the dose of 120 mg SC, every month denosumab is indicated for the prevention of SREs in patients with bone metastases from solid tumors, including prostate cancer. Several studies have been published for SRE prevention dosing regimen8.

The results of a randomized study on 1432 men with prostate cancer that received denosumab versus placebo have demonstrated an increase in bone metastasis-free survival9. In this phase III, double-blind, randomized study, denosumab significantly increased bone metastasis-free survival by a median of 4.2 months (29.5 vs 25.2). In particular, the primary endpoint of the study was bone metastasis-free survival, a composite endpoint determined by time to first occurrence of bone metastasis or death from any cause. The overall survival was similar between the two groups as well as the rate and grade of adverse effects except for hypocalcemia (2% vs <1%), while the jaw osteonecrosis (5% vs 0%) was higher in denosumab group.

These results upon the incidence and delay of SRE onset in patients with bone metastases have been confirmed by a recent meta-analysis of six controlled studies including 6,142 patients with breast cancer, prostate cancer, solid tumors except from lung cancer and myeloma9. Furthermore, nine (95% CI 7–11) additional people need to be treated to prevent one SRE, suggesting that this difference is clinically significant, given the morbidity and costs associated with SRE9.

Many recent studies reported a significant superiority of denosumab versus zoledronic acid in delaying SREs and in pain and health-related quality of life11, 12. These studies support the early initiation of denosumab when patients present with bone metastases, including asymptomatic bone metastases, to delay SREs and the onset of worse pain or use of strong opioids12.
A study conducted by 342 centers compared denosumab (120 mg SC) with zoledronic acid (4 mg IV) documented the prevention of SREs in 1,904 men with bone metastases from mCRPC. The median time to first SRE was 20.7 months with denosumab and 17.1 months with zoledronic acid. Bone resorption markers such as urinary N-telopeptide were found to be significantly suppressed in the denosumab arm compared with the zoledronic acid arm (p <0.0001). The rate and grade of adverse effects was similar between the two groups. The authors concluded that denosumab was more effective than zoledronic acid. Furthermore, patient-level data from three identically designed, randomized, double-blind, active-controlled, phase III studies of patients with breast cancer, prostate cancer, other solid tumors or multiple myeloma were combined. Denosumab was found to be superior to zoledronic acid in delaying time to first SRE by a median 8.2 months and in reducing the risk of a first SRE by 17% (p <0.001).

The use of zoledronic acid has several limitations and inconveniences: Need for IV access and administration, monitoring of renal function, dose adjustment, on-study dose withholding and management of influenza-like syndrome. On the contrary, the aforementioned limitations do not apply to denosumab as it is administered SC, it has no effect on renal function and it is not associated with acute phase reactions. Other studies showed denosumab is a cost-effective treatment option for the prevention of SREs in patients with advanced solid tumors and bone metastases compared to zoledronic acid. The overall value of denosumab is based on superior efficacy, favorable safety, and more efficient administration.

Lastly, another recent study assessed the cost-effectiveness of denosumab vs zoledronic acid in bone-metastatic CRPC including the parameter of quality-adjusted life-years (QALYs). Denosumab resulted in fewer estimated SREs (-0.241), more QALYs (0.0074) and lower SRE-related costs (-$2,340), but higher drug-related costs ($10,181) and total costs ($7,841) versus zoledronic acid. The base case estimated cost per QALY-gained was $1,058,741.

According to EAU 2015 guidelines for “nonspecific” management of mCRPC, calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates.

Cabozantinib, a Met and VEGF - R2 inhibitor was recently tested in patients with metastatic CRPC. Impressive preliminary results from a phase II study that enrolled 168 patients in 2011 were recently reported, including notably a partial or complete improvement in the bone scan in 85% and pain improvement in 60% of the patients. Toxicity is as expected for a tyrosine kinase inhibitor, including fatigue, hypertension and palmar-plantar syndrome, and constitutes a challenge for the original 100 mg/day dose with respect to further development. A phase III trial was recently initiated with pain as the primary end-point and a global phase III trial with overall survival as the primary end-point in patients with metastatic CRPC failing docetaxel and abiraterone is also in the pipeline. Cabozantinib shows encouraging clinical activity in both bone and soft tissue metastatic lesions in CRPC patients and an overall disease control rate at week 12 of 74%.

**Radium 223**

Radium 223 is the first radiopharmaceutical agent to demonstrate improved survival among patients with symptomatic bone-metastatic CRPC. An α particle consist of two protons and two neutrons, a β particle is a high energy electron, while a γ ray is described as ionizing electromagnetic radiation. Each type of radiation has different advantages and disadvantages.

Alpha particles have the shortest range of these particle types, resulting in a dense deposition of energy close to the origin of the particle emission. Alpha particles can be stopped by a sheet of paper, eliminating the need for any radiation shielding. Radium 223, as an α emitter, administered intravenously requires no radiation safety precautions such as particular sleeping arrangements, limited time or specified distance from children or pregnant women. Given the excellent safety profile of Radium 223, there is interest in combination regimens with therapies such as abiraterone and enzalutamide.

Radium 223 was recently approved by the FDA in 2013 for the management of men with metastatic castrate resistant prostate cancer. In the ALSYMPCA phase III placebo controlled trial 922 men with symptomatic bone-metastatic CRPC were randomized using a 2:1 ratio to receive six injections every 4 weeks.
of either radium 223 (50 Kbq/kg) or placebo. Entry criteria included at least two bone metastases without visceral metastases and either prior docetaxel treatment or inability to receive docetaxel. The primary endpoint was overall survival, with secondary endpoints of time to first SRE, time to alkaline phosphatase progression, alkaline - phosphatase response, alkaline - phosphatase normalization, time to PSA progression, safety, and quality of life. Median survival was significantly increased from 11.2 months to 14.0 months with a hazard ratio of 0.695 in favor of radium 223. In addition, there was significant improvement in median time to SRE (13.6 months vs 8.4 months), time to alkaline phosphatase progression, and time to PSA progression (hazard ratio 0.671) favoring the treatment arm.

Adverse events (AEs) were determined for any man who received >1 injection in 762 patients. AEs were observed in 88% of the radium 223 patients and 94% of placebo - treated patients. Serious AEs were higher in the placebo group (43% vs 55%) and treatment discontinuation due to AEs was higher in the placebo group (13% vs 20%). Grade 3/4 hematologic toxicities were comparable between the two arms (neutropenia 3% vs 1%, thrombocytopenia 6% vs 2%, anemia 13% vs 13%). Given, that radium 223 is excreted via the intestinal system, which can manifest as diarrhea, nausea or vomiting, careful monitoring of the patient’s oral intake and fluid status is crucial to prevent dehydration.

**Abiraterone and Enzalutamide**

In the first St Gallen Advanced Prostate Cancer Consensus Conference 2015 (APCCC), which reviewed the areas of controversy in advanced prostate cancer management, the post - docetaxel use of abiraterone or both pre - and post - docetaxel use of enzalutamide, showed a significant reduction in the time to first SRE in the active treatment arms.

Relevant studies demonstrated that abiraterone acetate had a minimal budget impact on health plans. A relevant advantage was the cost savings due to the lack of chemotherapy - related side effects as well as the ease of administration.

Exploratory analyses of COU - AA - 301 randomized trial, evaluating the impact of abiraterone on pain control, and skeletal - related events suggest abiraterone has efficacy in all these settings. In patients with clinically significant pain at baseline, abiraterone significantly increased the number of patients reporting palliation of pain (45% vs 28.8%; p= 0.0005), as well as faster palliation (median time to palliation 5.6 months vs 13.7 months; p= 0.0018). Median time to occurrence of first skeletal - related event (defined as pathologic fracture, spinal cord compression, or palliative surgery or radiation to bone) was also significantly longer in abiraterone treated patients (25 months versus 20.3 months; p= 0.0001).

**When should we initiate the bone protective agent?**

In a phase III study, 645 patients with castration sensitive prostate cancer and bone metastases, where randomized with immediate initiation of zoledronic acid versus zoledronic acid initiation after disease progression into castration resistant status. In conclusion, in men with castration - sensitive prostate cancer and bone metastases, early treatment with zoledronic acid was not associated with lower risk for SREs.

There is still not enough evidence for the use of denosumab for patients with castration sensitive prostate cancer. Nevertheless, an exploratory analysis in a global, randomized, placebo - controlled trial of men with high - risk non metastatic CRPC showed that denosumab increases time to first bone metastasis. Patients with shorter Prostate - Specific Antigen Doubling Time (PSADT) are at greater risk for bone metastasis or death. Denosumab consistently improves bone metastases free survival (BMFS) in men with shorter PSADT and time to first bone metastasis. OS and overall prostate cancer progression were similar between the placebo and denosumab groups.

Among men with PSADT ≤10 months, time to first bone metastasis was 6.4 months longer in the denosumab group than in the placebo group (32.4 vs 26 months). Denosumab reduced the risk of first bone metastasis by 15% (HR, 0.85; 95% CI, 0.71 to 1.01; P = 0.065). Among men with PSADT ≤6 months, time to first bone metastasis was 4.4 months longer in the denosumab group than in the placebo group (26.5 vs 22.1 months). Denosumab reduced the risk of first bone metastasis by 20% (HR, 0.80; 95% CI, 0.65 to
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Among men with PSADT ≤ 4 months, time to first bone metastasis was 8 months longer in the denosumab group than in the placebo group (26.4 vs 18.5 months). Denosumab reduced the risk of first bone metastasis by 29% (HR, 0.71; 95% CI, 0.55 to 0.91; p = 0.008).

**Side-effects of bone protective agents**

Most common early onset side-effect (first 3 days) that has been documented is a flu-like syndrome which is much more common with zoledronic acid. Hypocalcaemia, infectious side-effects and jaw necrosis are slightly commoner with denosumab. Osteonecrosis of the jaw (ONJ) is a serious adverse effect of denosumab administration. It is a type of avascular necrosis most commonly affecting the mandible characterized of exposed, necrotic bone in the oral cavity for more than 8 weeks. As ONJ is not widely accepted to be solely avascular necrosis, direct detrimental effects of denosumab on monocytes and macrophages could provide a novel comprehensive understanding of its pathophysiology. There are data suggesting that macrophages could well be the central factor in allowing the infection of the jaw to develop first, followed by the necrosis. Risk factors for ONJ include the use of a dental appliance, history of tooth extraction and less frequently poor oral hygiene. ONJ responds adequately to conservative treatment and just a few patients needed surgical resection. A meta-analysis of seven randomized controlled studies demonstrated that the increased risk of ONJ was not statistically significant between denosumab and bisphosphonate treatment. Before initiation of denosumab, patients should have a comprehensive dental examination. Recently, this recommendation has been added in the American Society of Clinical Oncology (ASCO) clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. Appropriate patient selection with close attention to dental health, supplementation with calcium and vitamin D are effective strategies to minimize the impact of adverse events.

Furthermore, the dosage of zoledronic acid must be based on renal function and is contraindicated when the creatinine clearance is less than 30ml/min, whereas denosumab is not excreted by the kidneys and can be administered even to patients on dialysis.

The most important grade 3 or higher toxicities associated with radium 223 were low myelosuppression (anemia, neutropenia, and thrombocytopenia) and low gastrointestinal rates (diarrhea, nausea, and vomiting).

**Conflicts of interest:**
The authors declared no conflicts of interest.
References


