REVIEW ARTICLE

Advances in prevention and treatment of bone metastases in prostate cancer. Role of RANK/RANKL inhibition

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KEYWORDS
Prostate cancer; Bone metastases; Zoledronic acid; RANK; RANKL; Denosumab

Abstract
Background: Bone metastases are a common complication of prostate cancer, so treatment and prevention are essential to slow the progression of the disease and the occurrence of skeletal related events (SREs), which have devastating consequences for the quality of life of patients. Summary of evidence: Bone metastases are characterized by increased bone turnover and altered balance between osteogenesis and osteolysis, with activation of the RANK and its ligand (RANKL). In patients with metastatic prostate cancer, bisphosphonates have been the bone-targeted agents most commonly used to date. Zoledronic acid has demonstrated efficacy in the reduction and delay of SREs in patients with bone metastases. Denosumab, a RANKL inhibitor, has been demonstrated to be superior to zoledronic acid in the prevention of SREs in castration-resistant prostate cancer (CRPC). Both agents are being considered, along with other new bone-targeted agents, for the prevention of bone metastases in patients with nonmetastatic CRPC, where denosumab has already demonstrated superiority over placebo. Conclusions: Denosumab and zoledronic acid prevent SREs in patients with prostate cancer and bone metastases. Denosumab also has a potential role in delaying bone metastases in nonmetastatic patients. Advances in the treatment of CRPC include an increasing focus on prevention of the progression of bone disease.

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Introduction

Prostate cancer is one of the most frequent malignant tumors. According to data provided by GLOBOCAN, the estimated incidence and mortality in Western Europe for 2008 were 904 new cases and 12 deaths per 100,000 population-year. In Spain, the estimated incidence and mortality for 2008 were 57 new cases and 10 deaths per 100,000 population-year. When a patient with prostate cancer develops metastases, the disease must be considered incurable and treatments should be directed toward palliative intent. This does not mean that a nihilistic attitude should be adopted when managing it; on the contrary, several therapeutic options are available both in the systemic treatment with antineoplastic agents, and in the supportive care management of bone metastatic sites, which are the most frequent ones in this type of cancer. The initial antineoplastic treatment for metastatic prostate cancer is androgen blockade or androgen deprivation therapy (ADT), which successfully decreases the prostate-specific antigen (PSA), and improves the quality of life and survival, although it is associated with an accelerated loss of bone mass. However, despite this initial success, the cancer will progress again in the vast majority of patients. Second-line hormone therapy is possible (anti-androgen withdrawal, ketoconazole, among others), but much less effective. When prostate cancer progresses after these treatments, it is considered castration resistant (CRPC). Nowadays, several pharmacological therapy options are available in such a situation. The docetaxel-prednisone treatment showed, in a clinical trial versus mitoxantrone-prednisone, a statistically significant improvement in overall survival, achieving a median of 19.2 months and, at present, improvements in new chemotherapeutic agents or new therapeutic targets show positive figures in terms of overall survival.

The following is an overview of the consequences of bone metastases from prostate cancer, the pathogenesis of the metastatic bone process and the therapeutic management of the above-mentioned metastases, placing special emphasis on the pharmacology, efficacy and the safety profile of denosumab, an antibody directed against the receptor activator of nuclear factor kappa-B ligand (RANKL), a key mediator of bone destruction.

Consequences of bone metastases

In most solid tumors, bones are one of the most common locations for metastasis, along with the liver and lungs. The location of bone metastases partly affects the patient’s symptomatology, quality of life and prognosis. Although bone metastases can occur in any patient with advanced stage cancer, some tumors have a higher risk, including breast, prostate, lung, kidney and thyroid cancers, among others. About 70% of patients with advanced prostate cancer develop bone metastases.

Bone metastases are associated with significant morbidity. The clinical consequences of these metastases are known as ‘skeletal-related event’ (SRE), and they include four types of complications: fracture, need for bone radiotherapy, need for bone surgery to help control pain and prevent an immediate fracture, and spinal cord
compression. One of the biological features (with its corresponding radiological translation) of bone metastases from prostate cancer is that they are predominantly osteoblastic metastases. Nevertheless, although bone density is increased, the bone affected by osteoblastic metastasis has a more fragile structure than normal. Therefore, although to a lesser extent than lytic bone metastases, plastic metastases also mean an increased fracture risk. SREs have a significant impact on the patient’s quality of life, and they are associated with shorter survival of prostate cancer, as well as with an increase in the intake of healthcare resources. This decreased quality of life is primarily due to the associated pain, which often requires an aggressive management with narcotic painkillers and radiation therapy and/or surgery (up to 40% of cases). Old age and/or the prevalence and severity of the patient’s comorbidities are the main risk factors for fatal outcomes following hip fracture. Furthermore, fractures involve a high intake of healthcare resources, due to both their high incidence rate and the possible complexities when managing them.

SREs are key measuring and valuing elements in efficacy studies of supportive care in patients with bone metastases. Thus, effectiveness is measured depending on the ability of these agents to reduce the number or to delay the onset of SREs.

**Bisphosphonates in treating bone metastases**

Bisphosphonates are synthetic analogs of endogenous pyrophosphate which are incorporated into the bone matrix in the areas that undergo active remodeling, promoting the apoptosis in osteoclasts. By reducing the osteolytic activities, bisphosphonates could also play a role by inhibiting tumor proliferation, by depriving the tumor of growth factors released during osteolysis, as some pre-clinical studies suggest. Zoledronic acid has proved to reduce SREs in patients with CRPC and bone metastases, whereas no data regarding other bisphosphonates are available. 643 patients with CRPC and bone metastases were randomly assigned in a phase III trial to receive intravenous zoledronic acid for 15 months, at a dosage of 4 mg every three weeks (Q3W), zoledronic acid at 8 mg Q3W (subsequently reduced to 4 mg due to toxicity), or placebo. The primary outcome measure was the percentage of patients with at least one SRE during the study. The results showed that patients receiving 4 mg zoledronic acid Q3W were less likely to suffer SREs compared to the placebo group (33.2 versus 44.2%; difference: −11.0%, a 95% confidence interval [CI]: −20.3−1.8%; p = 0.021). Moreover, patients receiving 4 mg zoledronic acid Q3W suffered fewer fractures (13.1% with at least one fracture compared to 22.1% in the placebo group; p = 0.015). The median time to the first SRE was higher in patients treated with zoledronic acid than in those receiving placebo (488 versus 321 days; p = 0.01). No differences in overall survival were observed between study groups. Bisphosphonates have also proved to be effective at preventing pain associated with CRPC bone metastases in some open trials, with response rates ranging between 70% and 80%.

Zoledronic acid is currently the only intravenous bisphosphonate approved for prevention of SREs in patients with CRPC. The recommended regimen is a 4 mg dose every 3 or 4 weeks, even though the best dosing interval is unclear. It is given by a single-dose intravenous infusion over no less than 15 min. It should be accompanied by calcium and vitamin D supplementation. The dose of zoledronic acid must be reduced in patients with impaired renal function (creatinine clearance 30–60 ml/min). The treatment is not recommended for patients with a creatinine clearance of less than 30 ml/min. Acute-phase responses with a range of symptoms including skeletal pain, fever, fatigue, and chills are frequent adverse events, which usually resolve within a few days. Patients should undergo dental evaluation before starting bisphosphonate therapy to prevent osteonecrosis of the jaw. A history of trauma, dental surgery or dental infection, as well as long-term use of intravenous bisphosphonates, increase the risk of this adverse effect.

**Role of RANK/RANKL in bone metastases**

Over 30 years ago, it was suggested that osteoclasts required osteoblast activity to carry out their osteolytic activity. However, it was not until 15 years later that two research teams separately identified the element which acts as a mediator in this process. This substance, called osteoprotegerin (OPG), is a 120 kDa protein which shares significant homology with the functional domain of those ligands included in the tumor necrosis factor receptor (TNF) family. Shortly afterwards, a molecule – RANK – whose activity is inhibited by OPG, was purified. RANKL is a cytokine that also belongs to the TNF family, and which is expressed on osteoblast membranes. Thus, the process is based on a paracrine mechanism (close positioning between ligand-secreting cells and cells with receptor–ligand interactions), in which RANKL is secreted by osteoblasts (or stromal cells) and binds to RANK in osteoclasts and osteoclast precursors to initiate a signal transduction pathway that stimulates osteoclast formation, activation and survival. All this ultimately leads to increased osteolytic activity. OPG, in turn, is able to bind RANKL, blocking it and inhibiting osteoclastic bone resorption. Thus, bone mineral density is the end result of an intricate series of balances at the cellular (osteoblast–osteoclast) and molecular (RANKL–OPG) levels.

The other signal transduction pathway involved in processes associated with bone lysis is the parathyroid hormone-related protein (PTHrP) pathway. Both pathways are interconnected, as shown in cases of giant cell tumor, where PTHrP increases RANKL expression in tumor stroma cells. At the same time, the relative balance between OPG and RANKL is determined by increased RANKL synthesis generated by PTHrP and other pro-resorptive cytokines.

Prostate cancer cells induce the production of bone matrix at metastasis level through a general but unbalanced increase of the bone remodeling process. Nevertheless, in their initial phase, tumor cells lead to an increase in osteoclastic activity and consequent bone resorption in a process that is mediated by the RANKL–OPG system. It has been experimentally proven that prostate cancer cells can increase RANKL synthesis in osteoblasts. Furthermore, the RANK–RANKL system showed, in preclinical models with
transgenic animals, carcinogenic potential on breast tissue through a hormonal mechanism.\(^{30,32}\)

For all of these reasons, drugs that act on the RANK system are becoming increasingly important as treatment measures in patients with bone metastases. Likewise, the possibility that signal transduction pathways associated with RANK and RANKL could be therapeutic targets of antineoplastic agents is a working hypothesis that is currently under development, although it is still at an early stage.\(^{33}\)

**Denosumab for treatment of bone metastases**

Denosumab is a IgG2 monoclonal antibody, consisting of 2 heavy chains and 2 light chains of the kappa subclass.\(^{34}\) Its origin is fully human and it binds RANKL with high affinity and specificity, competing with it for binding RANK. Thus, denosumab prevents RANK activation through RANKL and the subsequent activation of the associated signal transduction pathway (Fig. 1). Thus, since it has an anti-RANK mechanism of action, denosumab ultimately reduces bone resorption caused by metastatic lesions.

A randomized, double-blind, pivotal phase III trial compared denosumab versus zoledronic acid in patients with CRPC and bone metastases not previously treated with bisphosphonates.\(^{35}\) This study included 1901 patients who were randomized (1:1) to receive subcutaneous denosumab (120 mg) + intravenous placebo or (4 mg) intravenous zoledronic acid + subcutaneous placebo, every four weeks. The primary endpoint was time to first SRE (considering as such the appearance of pathological fracture, diagnosis of spinal cord compression, need for radiation therapy, or surgery to bone). The median time to first SRE was 20.7 months in the denosumab group and 17.1 months in the zoledronic acid group (relative risk: 0.82; 95% CI (0.71–0.95); \(p = 0.008\) for superiority testing). It was also observed that the risk of experiencing multiple SREs was reduced in the denosumab group (adjusted \(p = 0.008\)). There were no differences between the 2 groups in overall survival, time to disease progression, or incidence of osteonecrosis of the jaw, which in fact occurred rarely in both groups: 2% in the denosumab group versus 1% in the zoledronic acid group (\(p = 0.09\)). Hypocalcaemia was more common in patients treated with denosumab (13 versus 6% in the zoledronic acid group; \(p < 0.0001\)). Adverse events associated with acute-phase reactions were less common with denosumab (8 versus 18% in the zoledronic acid group; \(p < 0.0001\)).\(^{35}\) On the other hand, it was observed that 22% of zoledronic acid patients required dose adjustment because of reduced renal function, whereas no adjustment was required in the denosumab group.\(^{35}\) Table 1 shows the main differences in mechanisms of action, administration, and safety profiles between denosumab and zoledronic acid.

With regard to the evolution of pain, it was observed that a significantly lower percentage of patients who had no/mild pain at baseline experienced moderate/severe pain with denosumab, compared to zoledronic acid at each visit (\(p < 0.05\) at months 5, 6, 7, 12, 13, 14 and 15). The median
Table 1  Pharmacological characteristics and mechanisms of action of zoledronic acid and denosumab, both indicated in patients with solid tumor bone metastases.

|                          | Chemical composition | Mechanism of action                                                                 | Route of administration/frequency/unit dose | Dose adjustments in patients with renal dysfunction | Common adverse reactions  
<table>
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<tbody>
<tr>
<td>Zoledronic acid (Zometa®)</td>
<td>Chemical agent (bisphosphonate, synthetic analog on endogenous pyrophosphate)</td>
<td>Selective binding to the bone matrix and inhibition of the osteoclast activity after internalization by the same in sites of bone resorption</td>
<td>Intravenous (infusion for at least 15 min) Every 3--4 weeks 4 mg</td>
<td>It cannot be administered in patients with CrCl &lt; 30 ml/min The initial dose must be adjusted in patients with CrCl 30-60 ml/min The renal function must be monitored to all patients before every administration If renal function deteriorates, treatment must be interrupted and resumed when serum creatinine is again within 10% of the value at the start of the treatment</td>
<td>Frequent: Fever, flu-like syndrome, anemia, headache, conjunctivitis, nausea, vomiting, anorexia, bone pain, myalgia, arthralgia, generalized pain, kidney failure, hypophosphatemia, increased blood creatinine and urea, hypocalcemia Of special interest: Alteration of the renal function (frequent) Mandibular osteonecrosis (little frequent) Acute-phase reactions (frequent) Atypical femur fractures (rare)</td>
</tr>
<tr>
<td>Denosumab (XGEVA®)</td>
<td>Specific fully human monoclonal antibody against RANKL</td>
<td>Specific binding to RANKL, which prevents activation of the RANK receptor on the surface of osteoclasts and their precursors, inhibiting the formation, function, and survival of these two cell types</td>
<td>Subcutaneous Every 4 weeks 120 mg</td>
<td>No dose adjustment is required in patients with renal failure The experience in patients undergoing CrCl &lt; 30 ml/min is limited It is not necessary to perform renal control when receiving denosumab</td>
<td>Frequent: Dyspnea, diarrhea, hypophosphatemia, dental extraction, hyperhidrosis Of special interest: Hypocalcemia (9.6%) Mandibular osteonecrosis (1.8%) Severe cellulitis with hospitalization (0.9%)</td>
</tr>
</tbody>
</table>

CrCl: creatinine clearance.
time to worsening of pain (>4 points score according to the Brief Pain Inventory-Short Form [BPI-SF]), which assesses the severity of pain on a scale of 1–10) in patients with no/mild pain at baseline was 177 days with denosumab versus 148 days with zoledronic acid (p = 0.142). It was also observed that fewer patients assigned to denosumab, who were taking no or mild painkillers at baseline, started strong opioid use during the course of the study compared with zoledronic acid.

In patients with cancer and bone metastases previously treated with bisphosphonates denosumab appeared to be more effective than zoledronic acid in terms of decreased N-telopeptide levels, as shown in a randomized phase II trial that included 111 patients, 50 of whom had prostate cancer. The importance of this last study is that it offers a pharmacodynamic basis for the clinically observed differences between both drugs for clinical endpoints, where denosumab provides additional benefit over zoledronic acid, which is the current standard treatment (Fig. 2).

Thus, considering those benefits demonstrated in the pivotal trial on prostate cancer, as well as in the other 2 phase III trials enrolling patients with breast cancer and other solid tumors or multiple myeloma, denosumab (XGEVA®, AMGEN Inc.) was approved by the American (FDA) and European (EMA) regulatory agencies, with the following indication: prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with bone metastases from solid tumors.

The latest American (National Comprehensive Cancer Network [NCCN]), European (European Association of Urology [EAU] guidelines), and Spanish (Grupo Español de Oncología Genitourinaria [SOGUG]) clinical practice guidelines recommend the use of both zoledronic acid and denosumab to prevent or delay SREs in patients with CRPC and bone metastases, and acknowledge the clinical benefits and tolerability of denosumab when compared with zoledronic acid (Table 2).

Prevention of bone metastases in non-metastatic prostate cancer

Since metastatic cells in prostate cancer have a predilection for bone tissue, the antitumour and antimetastatic effects of diverse bone-targeted agents in non-metastatic patients is currently being investigated, either administered as a single agent or in combination with other antitumour agents to try to delay the progression of the disease.

Several studies, based on positive results observed at preclinical levels, are assessing the antitumour activity of bisphosphonates. The clinical trials underway are the following: the Randomized Androgen Deprivation and Radiotherapy (RADAR) trial, the Zometa European Study, NTR355 (ZEUS), and the Systemic Therapy in Advancing or Metastatic

Figure 2  Delayed onset of SRE in prostate cancer patients and bone metastases treated with zoledronic acid (current standard treatment) or with denosumab: denosumab provides clinically relevant additional benefit. Data published in:  

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median time until the first SRE (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10.7</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>16.3</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>17.1</td>
</tr>
<tr>
<td>Denosumab</td>
<td>20.7</td>
</tr>
</tbody>
</table>

Data published in a Fizazi K et al., Lancet 2011; 377 (9769): 813-22  
Data published in b Saad F, et al.

Figure 3  Future treatment strategies in patients with castration-resistant prostate cancer and bone metastases: in all of them, early initiation of bone-targeted agents is recommended for the prevention or delay of skeletal-related events.
Table 2  Recommendations of the main clinical guidelines on prostate cancer on prevention of skeletal related events in patients with bone metastases.

<table>
<thead>
<tr>
<th>NCCN 2011 v4</th>
<th>EAU</th>
<th>SOGUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional systemic therapy for recurrent prostate cancer after castration (CRPC)</td>
<td>Recommendations on the palliative treatment of CRPC</td>
<td>Bone-directed therapies</td>
</tr>
<tr>
<td>In case of positive studies for metastasis: denosumab (category 1) or zoledronic acid (category 1) if there was bone metastasis</td>
<td>The patients with symptomatic and extensive bone metastases do not benefit from medical treatment in terms of prolongation of life (grade A)</td>
<td>As bone-directed therapies, we recommend zoledronic acid (4 mg IV every 3–4 weeks) or denosumab (120 mg SC every 4 weeks) for the treatment of bone metastases in patients with CRPC to prevent bone complications (level of evidence: IB, grade of recommendation: A) (both in first-line treatment options and in second-line options)</td>
</tr>
<tr>
<td>In men with CRPC and bone metastases, it has been shown that denosumab and zoledronic acid prevent SRE</td>
<td>The treatment should focus on improving the quality of life and, particularly, on reducing pain (grade A)</td>
<td></td>
</tr>
<tr>
<td>Compared to zoledronic acid, denosumab proved to be superior in SRE prevention</td>
<td>An effective medical treatment with maximum efficiency and low frequency of side effects is the main goal of the treatment (grade A)</td>
<td></td>
</tr>
<tr>
<td>The choice of agent depends on the underlying comorbidities, previous treatment with zoledronic acid, logistics, and/or costs</td>
<td>The use of bisphosphonates can be offered to patients with bone masses (we have mainly studied zoledronic acid) to prevent bone complications. However, the benefits must be balanced with the toxicity of these drugs; in particular, mandibular osteonecrosis must be avoided (grade A)</td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid is administered IV every 3–4 weeks. The dosage is based on predose serum creatinine, and it must be adjusted in cases of renal failure. It is not recommended if CrCl &lt; 30 ml/min</td>
<td>Denosumab can be offered as it has proved to delay/prevent SREs and it also increases the time to the first or subsequent SRE under study. Before the treatment, the patient must be advised about the potential benefits and side effects (toxicity), and especially mandibular osteonecrosis (grade A)</td>
<td></td>
</tr>
<tr>
<td>Denosumab is administered SC every 4 weeks. While renal control is not mandatory, it is not recommended if CrCl &lt; 30 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When the CrCl is &lt; 60 ml/min, the risk of severe hypocalcemia increases. All the patients will have to be treated with vitamin D and calcium and undergo regular monitoring of serum calcium</td>
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<tr>
<td>With both agents, we have observed cases of mandibular osteonecrosis; the risk increases in patients with tooth extraction, poor dental hygiene, or with dental appliances</td>
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<tr>
<td>The optimal duration of the therapy is uncertain</td>
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<tr>
<td>The toxicity profile of denosumab in patients who were already treated with zoledronic acid is uncertain</td>
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<tr>
<td>A role is being evaluated for zoledronic acid or denosumab in men starting androgen deprivation therapy due to bone metastases</td>
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Prostate Cancer: Evaluation of Drug Efficacy, NCT00268476 (STAMPEDE) trial.

Due to the key role of RANKL in the pathophysiology of bone metastases from prostate cancer,\textsuperscript{49,50} denosumab is also being investigated for its ability to delay the appearance of those metastases in patients with non-metastatic cancer. In that context, a phase-III trial, which randomized 1432 patients with HDT-resistant tumors and a high risk of developing bone metastases (PSA ≥ 8, or PSA doubling time ≤ 10 months, or both) to denosumab and placebo, was carried out. The results showed that denosumab significantly prolonged bone metastasis-free survival (median time 29.5 versus 25.2 months; relative risk: 0.85; CI 95%: 0.73–0.98; \( p = 0.032 \)), with a particularly relevant benefit in the subgroup of patients with PSA doubling time < 6 months.\textsuperscript{51} Symptomatic bone metastases were reported in 10% of patients with denosumab versus 13% in those treated with placebo (\( p = 0.03 \)), overall survival was similar. Adverse events were similar in both groups, except those regarding osteonecrosis of the jaw and hypocalcemia, which were more frequently observed in the denosumab group (5 and 2% respectively) than in the placebo group (0 and <1% respectively).\textsuperscript{53}

Other promising bone-targeted drugs are radioisotopes such as Radium 223 (alpharadin)\textsuperscript{65} and endothelin-1 (ET-1) receptor antagonists, which block the action of ET-1 (a powerful vasoconstrictive peptide), so they inhibit osteoblastic proliferation and bone formation, as well as reducing the proliferation of human prostate cancer cells.\textsuperscript{66,67} Atrasentan and zibotentan are the two ET-1 inhibitors under development (Table 3). Nevertheless, in a phase III clinical trial atrasentan did not obtain positive clinical results,\textsuperscript{68} although some biological response was shown, and two of the zibotentan trials have also been negative (Table 3).\textsuperscript{69}
<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug under study</th>
<th>Control group</th>
<th>Number of patients</th>
<th>Population</th>
<th>Design/duration</th>
<th>Main variable</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saad et al.\textsuperscript{30,31}</td>
<td>Denosumab (4 mg u 8 mg every 3 weeks)</td>
<td>Placebo</td>
<td>643</td>
<td>Patients with hormone-refractory prostate cancer with bone metastases</td>
<td>Randomization 1:1</td>
<td>Percentage of patients with ≥ 1 SRE after 15 months</td>
<td>33.2% patients with SRE zoledronic acid 4 mg vs 44.2% placebo (p = 0.021) Median up to the first SRE 488 days zoledronic acid 4 mg vs 321 days placebo (p = 0.01) Median: 20.7 months denosumab vs 17.1 months zoledronic acid HR denosumab vs zoledronic acid: 0.82 (95% CI: 0.71 to 0.95, p no-inferiority = 0.0002; p superiority = 0.008) Median: 14.0 months radio-223 vs 11.2 months placebo HR radium-223 vs placebo: 0.699 (95% CI: p = 0.0022) Finished prematurely due to significant benefits with respect to placebo in pre-specified intermediate analysis Negative: non-significant differences: Median: 14.0 months atrasertan vs 11.2 months placebo HR atrasertan vs placebo: 0.699 (p = 0.288) Slower increase of BAP and PSA with atrasertan versus placebo - (underway; planned recruitment end: March 2014)</td>
</tr>
<tr>
<td>Fizazi et al.\textsuperscript{55}</td>
<td>Denosumab (120 mg SC every 4 weeks)</td>
<td>Zoledronic acid (4mg IV every 4 weeks)</td>
<td>1901</td>
<td>Patients with hormone-refractory prostate cancer with bone metastases</td>
<td>Randomization 1:1</td>
<td>Time to the first SRE during the study</td>
<td>68.6% patients with SRE zoledronic acid 4 mg vs 55.3% placebo (p = 0.049) Median up to the first SRE 488 days zoledronic acid 4 mg vs 321 days placebo (p = 0.01) Median: 20.7 months denosumab vs 17.1 months zoledronic acid HR denosumab vs zoledronic acid: 0.88 (95% CI: 0.71 to 0.97, p no-inferiority = 0.005; p superiority = 0.008) Median: 14.0 months radio-223 vs 11.2 months placebo HR radium-223 vs placebo: 0.767 (95% CI: p = 0.002) Finished prematurely due to significant benefits with respect to placebo in pre-specified intermediate analysis Negative: non-significant differences: Median: 14.0 months atrasertan vs 11.2 months placebo HR atrasertan vs placebo: 0.699 (p = 0.288) Slower increase of BAP and PSA with atrasertan versus placebo - (underway; planned recruitment end: March 2014)</td>
</tr>
<tr>
<td>ALSYMPCA\textsuperscript{65} (NCT00699751)</td>
<td>Radium-223 (alpharadin) (6 cycles of 50 kBg/kg every 4 weeks)</td>
<td>Placebo</td>
<td>900 (planned)</td>
<td>Patients with hormone-refractory prostate cancer with at least 2 bone metastases and without visceral metastases</td>
<td>Randomization 2:1 (placebo) 3 years</td>
<td>Patient survival</td>
<td>32.1% patients with SRE radium-223 64 mg vs 37.8% placebo (p = 0.05) Median up to the first SRE 488 days radium-223 64 mg vs 321 days placebo (p = 0.01) Median: 20.7 months radium-223 vs 17.1 months placebo Median: 14.0 months radium-223 vs 11.2 months placebo HR radium-223 vs placebo: 0.90 (95% CI: p = 0.0023) Finished prematurely due to significant benefits with respect to placebo in pre-specified intermediate analysis Negative: non-significant differences: Median: 14.0 months atrasertan vs 11.2 months placebo HR atrasertan vs placebo: 0.699 (p = 0.288) Slower increase of BAP and PSA with atrasertan versus placebo - (underway; planned recruitment end: March 2014)</td>
</tr>
<tr>
<td>Carducci et al.\textsuperscript{68}</td>
<td>Atrasertan (10 mg oral daily)</td>
<td>Placebo</td>
<td>809</td>
<td>Patients with hormone-refractory prostate cancer with bone metastases</td>
<td>Randomization 1:1</td>
<td>Time free of progression</td>
<td>44.2% patients with SRE atrasertan 10 mg vs 37.8% placebo (p = 0.08) Median up to the first SRE 488 days atrasertan 10 mg vs 321 days placebo (p = 0.01) Median: 20.7 months atrasertan vs 17.1 months placebo Median: 14.0 months atrasertan vs 11.2 months placebo HR atrasertan vs placebo: 0.90 (95% CI: p = 0.0023) Finished prematurely due to significant benefits with respect to placebo in pre-specified intermediate analysis Negative: non-significant differences: Median: 14.0 months atrasertan vs 11.2 months placebo HR atrasertan vs placebo: 0.699 (p = 0.288) Slower increase of BAP and PSA with atrasertan versus placebo - (underway; planned recruitment end: March 2014)</td>
</tr>
<tr>
<td>SWOG 0421 (NCT00134056)</td>
<td>Atrasertan (10 mg oral daily) + docetaxel-prednisone</td>
<td>Placebo + docetaxel-prednisone</td>
<td>930 (planned)</td>
<td>Patients with hormone-refractory prostate cancer with bone metastases without previous treatment with taxanes</td>
<td>Randomization 1:1</td>
<td>Time free of progression and overall survival</td>
<td>37.1% patients with SRE atrasertan 10 mg vs 37.8% placebo (p = 0.08) Median up to the first SRE 488 days atrasertan 10 mg vs 321 days placebo (p = 0.01) Median: 20.7 months atrasertan vs 17.1 months placebo Median: 14.0 months atrasertan vs 11.2 months placebo HR atrasertan vs placebo: 0.90 (95% CI: p = 0.0023) Finished prematurely due to significant benefits with respect to placebo in pre-specified intermediate analysis Negative: non-significant differences: Median: 14.0 months atrasertan vs 11.2 months placebo HR atrasertan vs placebo: 0.699 (p = 0.288) Slower increase of BAP and PSA with atrasertan versus placebo - (underway; planned recruitment end: March 2014)</td>
</tr>
<tr>
<td>Reference</td>
<td>Drug under study</td>
<td>Control group</td>
<td>Number of patients</td>
<td>Population</td>
<td>Design/duration</td>
<td>Main variable</td>
<td>Results</td>
</tr>
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<tr>
<td>ENTHUSE M1 Estudio 14 (NCT00554229)</td>
<td>Zibotentan (10 mg oral daily)</td>
<td>Placebo</td>
<td>848 (planned)</td>
<td>Patients with hormone-refractory prostate cancer with bone metastases; without pain or with mild pain</td>
<td>Randomization 1:1 Duration oriented to events</td>
<td>Overall survival</td>
<td>NEGATIVE: Without significant differences in overall survival (unpublished data)</td>
</tr>
<tr>
<td>ENTHUSE M1C Study 33 (NCT00617669)</td>
<td>Zibotentan (10 mg oral daily) + docetaxel</td>
<td>Placebo + docetaxel</td>
<td>1445 (planned)</td>
<td>Patients with hormone-refractory prostate cancer with bone metastases; without previous treatment with chemotherapy</td>
<td>Randomization 1:1 Duration oriented to events</td>
<td>Overall survival</td>
<td>- (underway; planned recruitment end: May 2012)</td>
</tr>
<tr>
<td>CA180-227 (NCT00744497)</td>
<td>Dasatinib + docetaxel-prednisone</td>
<td>Placebo + docetaxel-prednisone</td>
<td>1500 (planned)</td>
<td>Patients with hormone-refractory prostate cancer with bone metastases</td>
<td>Randomization 1:1 Duration oriented to events</td>
<td>Overall survival</td>
<td>- (underway; planned recruitment end: December 2012)</td>
</tr>
<tr>
<td>Prevention or delay of bone metastases in non-metastatic prostate cancer</td>
<td>Smith et al.13</td>
<td>Denosumab (120 mg SC every 4 weeks)</td>
<td>Placebo</td>
<td>Patients with non-metastatic hormone-refractory prostate cancer with at least one risk factor for bone Mtx (PSA ≥ 8 and/or PSA binding ≤ 10 months)</td>
<td>Randomization 1:1 Duration oriented to events</td>
<td>Time free of bone metastases</td>
<td>Median: 29.5 months denosumab vs 25.2 months placebo RR denosumab vs placebo: 0.85 (95% CI: 0.73 to 0.98, p = 0.032)</td>
</tr>
<tr>
<td>ZEUS (NTR355)</td>
<td>Zoledronic acid (4 mg IV every 3 months)</td>
<td>Placebo</td>
<td>1433 (planned)</td>
<td>Patients with non-metastatic hormone-refractory prostate cancer with at least one risk factor for bone Mtx (PSA ≥ 20 and/or nodal Mtx and/or Gleason index ≥ 8)</td>
<td>Randomization 1:1 48 months of follow-up</td>
<td>% patients with bone metastases at 48 months</td>
<td>- (underway)</td>
</tr>
</tbody>
</table>
Future treatment strategies for prostate cancer

A significant number of new drug therapies are currently being investigated in patients with CRPC. As stated in the paragraph above, diverse bone-targeted drugs (bisphosphonates, denosumab, ET-1 receptor antagonists) are under evaluation both for SRE prevention in metastatic patients and for prevention of bone metastases in those patients who have not yet developed them (Table 3).

As far as new antitumor agents are concerned, several studies are evaluating the effectiveness of docetaxel in combination with anti-angiogenic drugs such as bevacizumab, aflibercept, or lenalidomide, as well as docetaxel combinations with drugs with new mechanisms of action such as OGX-011 (custirsten, anti-clusterin, pro-apoptotic), DN-101 (high-dose calcitriol) or dasatinib (a SRC tyrosine kinase inhibitor). New non-docetaxel based regimens include chemotherapy drugs such as cabazitaxel or hormonal treatment with abiraterone, both approved in patients refractory to docetaxel according to results of randomized trials. Other agents that should be considered promising, but still investigational, are new anti-angiogenic drugs such as tasquinimod, immunotherapeutic drugs such as sipuleucel-T, already approved by the FDA, and new antiandrogenic drugs such as TAK-700 (orteronel) and MDV3100 (enzalutamide), the latter with recently-published positive results.

Whatever the role of these new promising agents in the near future of prostate cancer treatment, management of these patients should always consider the inclusion of a treatment for the prevention of SREs, considering the increased risk and their devastating clinical consequences (Fig. 3). Under this scenario, denosumab seems to be the drug that currently provides better clinical outcomes while offering a good safety profile. Therefore, it would be the optimal candidate when choosing an antiresorptive treatment in future studies with new antitumor agents. It is still to be determined if combined denosumab and some of these new agents administration could offer a synergic or additive effect in patients with prostate cancer.

Conclusions

Bone metastases have great clinical significance in prostate cancer, since they are highly frequent and explain much of morbidity and mortality in later stages of the disease. The pathogenesis of those metastases, with increased bone turnover and altered balance between osteogenesis and osteolysis, provides increased justification for the use of bone-targeted agents for their prevention and treatment. Among those agents, zoledronic acid has shown its efficacy in reducing and delaying SREs in metastatic patients, and it is being evaluated for a delayed appearance of bone metastases. Up to now, denosumab is the only approved RANKL inhibitor that has demonstrated superiority over zoledronic acid in preventing SRE in patients with metastatic CRPC. Besides, it has the potential to delay bone metastases in non-metastatic patients, where it has already demonstrated superiority versus placebo, so it could be a new potential therapeutic option. Other new bone-targeted agents or
with an antitumor effect, such as ET-1 receptor antagonists, tyrosine kinase inhibitors, anti-angiogenic, antiandrogenic, immunotherapeutic, or radiopharmaceutical agents, either alone or in combination, can significantly change the treatment of CRPC and bone metastases treatment in the near future.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**


