

REVIEW ARTICLE

Current therapeutic options targeting bone metastasis in metastatic castration resistant prostate cancer

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Summary

Prostate cancer is a major public health problem worldwide, still remaining the most common cancer among elder males in both Europe and USA, being responsible for approximately 30,000 deaths in USA in 2014. Nowadays, after decades of basic research, novel treatment options have emerged focusing on men suffering from metastatic castration-resistant prostate cancer improving overall survival. It is also estimated that more than 90% of such patients develop bone metastasis, resulting in a signifi-

cant increase in morbidity and mortality. The purpose of this review was to discuss the treatment options targeting bone metastasis in castration-resistant prostate cancer patients by examining the available literature focusing primarily in the role of zoledronic acid, denosumab and radium 223.

Key words: castration-resistant prostate cancer, denosumab, skeletal related events, radium 223, zoledronic acid

Introduction

Prostate cancer is a major public health problem worldwide, still remaining the most common cancer among elder males in both Europe and USA, being responsible for approximately 30,000 deaths in USA in 2014 [1,2]. Although non-palpable prostate cancer now represents about 60-75% of newly diagnosed cases, it is estimated that 10-20% of prostate cancer patients initially present with metastatic disease [3]. Moreover, up to one-third of patients who initially presented at an early stage will eventually develop disease recurrence despite early definite treatment [3]. Primary androgen deprivation therapy achieved either by surgical castration or by pharmaceutical agents is the standard of care in patients initially diagnosed with metastatic disease leading in over 80% of the cases to clinical improvement and reduction of serum prostate specific antigen (PSA) levels [4]. However, almost all advanced metastatic cancers treated with androgen deprivation will eventually develop into castration-resistant prostate cancer

(CRPC) with more than 90% of the patients with metastatic castration-resistant prostate cancer (mCRPC) developing bone metastasis which results in a significant increase in morbidity and mortality [5]. Patients at this stage of disease may be clinically asymptomatic or may present with bone pain or even skeletal-related events (SRE) which include manifestations of spinal cord compression, pathological fractures, hypercalcemia of malignancy, requirement for interventions such as bone surgery, or need for bone radiation [6]. More specifically in the absence of bone targeted therapy the rate of SRE at 15 months was reported to be 44%, including a 22% rate of bone fracture [7]. Traditionally, the bone lesions in mCRPC have been described mostly as osteoblastic but increasing evidence lends credence to the importance of osteolytic factors in prostate cancer metastasis. It is now proved fact that in an osteoblastic metastasis as well as the adjacent bone there is an increase in osteoclast number and activity which

brings evidence of both an osteolytic and an osteoblastic component with increased bone formation and resorption [8,9]. From 2004 until 2010 only docetaxel was approved as therapeutic option for mCRPC as it was the sole treatment demonstrating a survival advantage, with cabazitaxel being a second line option when primary treatment with docetaxel failed [10]. Nowadays new drugs are approved for mCRPC such as sipuleucel-T, abiraterone acetate [29] and enzalutamide as well as bone targeted therapies such as the radioactive radium 223 dichloride, denosumab and zoledronic acid (Table 1) [11,12].

This review discusses the role of these bone targeted therapies in the everyday practice in the current treatment of bone metastasis in mCRPC and the benefits in patients' morbidity and mortality.

Table 1. Approved therapeutic options for metastatic, castration-resistant prostate cancer

Chemotherapy	Docetaxel Cabazitaxel
CYP17A Inhibitor	Abiraterone
Androgen Receptor Inhibitor	Enzalutamide
Immunotherapy	Sipuleucel-T
α Particle Emitter	Radium 223
Biphosphonate	Zoledronic Acid
Monoclonal Antibody	Denosumab

Zoledronic acid

Zoledronic acid is a nitrogen-containing biphosphonate, currently used for the prevention of SREs in patients suffering from mCRPC. Its approval by FDA in 2002 was made after the conclusion of an international phase III randomized placebo-controlled trial of zoledronic acid in patients with hormone refractory metastatic prostate carcinoma [7] (Table 2). The trial enrolled a total of 643 asymptomatic patients not receiving chemotherapy during the time of the enrolment but eligible to be treated with such therapy during the study. All patients were randomly assigned to receive treatment either with zoledronic acid in a dose of 4 or 8 mg, or placebo once every 3 weeks for 20 cycles lasting 15 months. The primary endpoint of the study was the diagnosis of at least one SRE. Patients were monitored by bone scans performed at 6 and 15 months after the enrollment. Moreover, follow-up bone surveys were conducted every 3 months. As a result, at least one SRE was diagnosed in 44.2% of the patients in the placebo group vs 33.2% in the zoledronic acid

group receiving 4 mg dose (95% confidence interval -20.3 to -1.8; $p=0.021$) and in 38.5% of patients receiving zoledronic acid initially 8 mg followed by reduction at 4 mg due to an observed later renal toxicity (95% confidence interval -15.1 to 3.6; $p=0.222$). On the other hand, no statistically significant difference was noted between the groups in terms of analgesic scores, overall quality of life, disease progression and performance status. As for side effects, the most commonly observed in the zoledronic group arm were fatigue, anemia, myalgia, fever and lower limb edema although no difference in discontinuation of the treatment was noted between the groups [7]. In 2004 Saad et al. published the long term results of their original trial which showed that zoledronic acid managed to reduce SREs by 36% compared with placebo at 24 months of follow up with the median time to first SRE being 488 days in the zoledronic acid arm vs 321 days in the placebo arm ($p=0.002$) [13] (Table 2). Although zoledronic acid is well tolerated, 1% of the patients present with osteonecrosis of the jaw with poor dental hygiene, dental interventions and frequency and duration of use described as risk factors [14]. Length of exposure seems to be the most important risk factor for this complication [15]. It is therefore very important that all patients scheduled to receive zoledronic acid to obtain a baseline dental evaluation prior

Table 2. Major trials for current bone targeted therapies

Reference	Intervention	Results
Saad et al [7]	Zoledronic acid 8 or 4 mg vs placebo	SRE at 15 months: 38.5% ZA vs 44.2% placebo Time to first SRE: 363 days ZA vs 321 days placebo
Saad et al [13] (follow up)	Zoledronic acid 4 mg vs placebo	SRE at 24 months: ZA 38% vs 49% placebo Time to first SRE: ZA 488 days vs 321 days placebo
Fizazi et al [18]	Denosumab 120mg vs zoledronic acid 4 mg	Time to first SRE was reduced by 3.6 months in the denosumab arm
Smith et al [20]	Denosumab 120 mg vs placebo	Denosumab has increased bone metastasis free survival by 4.2 months
Parker et al [23]	Radium 223 vs placebo	Median survival: 14 months RA vs 11.2 months placebo Median time to first SRE: 13.6 months RA vs 8.4 placebo

SRE: skeletal related events, ZA: zoledronic acid, RA: radium 223

to the initiation of therapy and avoid major dental procedures if possible.

Denosumab

Denosumab is a fully humanized monoclonal antibody which suppresses the formation of osteoclast by binding to receptor activator of nuclear factor κ B ligand (RANK-L) [16]. More specifically, receptor activator of nuclear factor κ B (RANK) is an important molecule in bone homeostasis. It is activated by RANK-L, a member of the tumor necrosis factors family, and therefore stimulates osteoclast formation, differentiation, activation, adherence and survival eventually leading to bone resorption [17] (Figure 1). Denosumab was FDA-approved in 2010 as a therapeutic option for prevention of SREs in patients suffering from bone metastasis from solid tumors including prostate cancer.

Denosumab proved its superiority over zoledronic acid in terms of preventing SREs in men with mCRPC suffering from bone metastasis after the completion of a phase III randomized double blind study including a total of 1904 patients [18] (Table 2). Patients were 1:1 randomized to receive either 120 mg denosumab or 4mg zoledronic acid every 4 weeks with primary endpoint of the study the time to first SRE. Median time to first SRE was 20.7 months in the denosumab arm compared to 17.1 months in the zoledronic acid arm ($p=0.008$ for superiority). No differences were noted between the two groups in terms of overall survival or disease progression. In addition, the adverse effect profile was similar with most common adverse events being anemia, decreased appetite, nausea, bone pain fatigue and back pain. Osteonecrosis of the jaw was reported in 2% in the denosumab arm compared to 1% in the zoledronic acid arm [18]. This trial led to the FDA approval of denosumab with the indication of preventing SREs in men suffering from metastatic prostate cancer. In a further analysis of this phase III study by Smith et al., denosumab reduced the risk of skeletal complications vs zoledronic acid regardless of whether the endpoint of the study was defined as time to first SRE or incidence of symptomatic skeletal events (SSE) which include symptomatic pathologic fractures, surgery to bone, radiation to bone or symptomatic spinal cord compression ($p=0.004$) [19].

Furthermore, a phase III randomized placebo-controlled trial evaluated the efficacy of denosumab in improving metastasis-free survival in mCRPC patients. Patients were randomly assigned

(1:1) via an interactive voice response system to receive subcutaneous denosumab 120 mg or subcutaneous placebo every 4 weeks. Randomization was stratified by PSA eligibility criteria and previous or ongoing chemotherapy for prostate cancer. The primary endpoint was bone metastasis-free survival, determined by time to first occurrence of bone metastasis or death from any cause. Therapy with denosumab was associated with an increase of bone metastasis-free survival by 4.2 months compared to placebo. No statistically significant difference was noted in prostate cancer progression, overall survival, progression-free survival and adverse events between the two groups [20] (Table 2). In addition, Smith et al. in a follow up study evaluated the results of denosumab administration in bone metastasis-free survival by explanatory analyses by baseline PSA doubling time and as a result denosumab was associated with an improvement in bone metastasis-free survival in patients with shorter PSA doubling time [21].

As both zoledronic acid and denosumab treatment reduces SREs there is a need of determining the safety of prolonged therapy. The results of extended denosumab therapy in patients with bone metastases are described from the open-label extension phase of two phase 3 trials. During the blinded treatment phase, exposure-adjusted incidences of osteonecrosis of the jaw were 1.9 % and 1.2 % in the denosumab and zoledronic acid groups respectively. Moreover, the vast majority of osteonecrosis of the jaw cases was associated with the already established risk factors such as major dental procedures, poor oral hygiene and prolonged duration of therapy. As a result, these data from the open-label extension phase of two pivotal trials in metastatic breast and prostate cancer confirm the known safety profile of denosumab with long-term administration for a median 12.0 months (up to 5.6 years) in metastatic prostate cancer. Additionally, there were no new safety signals among patients who underwent treatment with denosumab after previous zoledronic acid therapy, suggesting that changing from bisphosphonate to denosumab is a feasible and safe option. Patients should continue to be counseled on the importance of dental hygiene as well as adherence to calcium and vitamin D supplements while receiving bone-targeted therapy [22,23]. As far as hypocalcemia associated with denosumad use is concerned, it has been noted that severe hypocalcemia is observed in patients with high levels of baseline alkaline phosphatase (ALP) and high performance status [24].

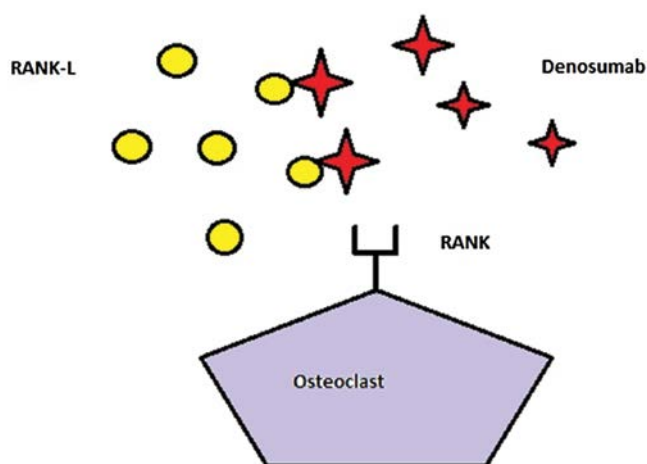


Figure 1. Mechanism of denosumab action: denosumab binds to RANK –L inhibiting RANK activation.

Radium 223 dichloride (Alpharadin)

Radium 223 is an α particle emitter administered intravenously with high affinity for the bone matrix. As alpha particles can be stopped by a sheet of paper, radium 223 requires no radiation safety precautions such as particular sleeping arrangements, limited time or specified distance from children or pregnant women. Radium 223 was recently approved by the FDA in 2013 for the management of men with mCRPC after the conclusion of a randomized phase III trial showing an overall survival benefit [25,26]. In this trial, 922 men with symptomatic bone-metastatic CRPC were randomized in a 2:1 ratio to receive either six injections every 4 weeks of radium 223 or placebo [25] (Table 2). The primary endpoint was overall survival, with secondary endpoints the 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 in the radium 223 arm (11.2 vs 14.0 months). Furthermore, an improvement in median time to SRE (13.6 vs 8.4 months), time to alkaline phosphatase progression, and time to PSA progression was recorded,

also favoring the radium 223 arm. Adverse events were detected in 88% of the radium 223 patients and 94% of the placebo-treated patients. Moreover, higher serious adverse events were reported in the placebo group (43 vs 55%) and treatment discontinuation due to them was also higher in the placebo group [24]. Moreover, Alpharadin was associated with significant and meaningful quality of life improvement as well as lower quality of life decline [27]. 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 [28]. The safety profile of radium 223 is encouraging in comparison to the β emitters, which may allow for increased dosing or combination with docetaxel chemotherapy or novel agents such as enzalutamide or abiraterone acetate [29].

Conclusion

Denosumab has proved superiority over zoledronic acid in terms of preventing SRE in mCRPC patients, has an easy way of administration by subcutaneous injection and can also be administered to patients with impaired renal function. In all cases where a patient is treated with denosumab, vitamin D supplements and calcium should be also administered in order to prevent hypocalcemia and patients should be advised to avoid major dental operations. Zoledronic acid still remains an alternative choice especially in cases where adequate insurance coverage is unavailable. Radium 223 is the first radiopharmaceutical to provide a prolongation in overall survival in men with CRPC cancer. It also prolongs the median time to first SRE when compared to placebo. Moreover, the safety profile is encouraging thus it becomes a valid option for symptomatic mCRPC patients with bone metastasis [30].

Conflict of interests

The authors declare no conflict of interests.

References

1. Arnold M, Karim-Kos HE, Coenbergh JW. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. *Eur J Cancer* 2015;51:1164-1187.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9-29.
3. Pound CR, Partin AW, Eisenberger MA et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591-1597.
4. Pagliarulo V, Bracarda S, Eisenberger MA et al. Contemporary role of androgen deprivation therapy for prostate cancer. *Eur Urol* 2012;61:11-25.

5. Costa L, Badia X, Chow E et al. Impact of skeletal complications on patients' quality of life, mobility and functional independence. *Supp Care Cancer* 2008;16:879-889.
6. So A, Chin J, Fleshner N et al. Management of skeletal related events in patients with advanced prostate and bone metastases: incorporating new agents into practice. *Can Urol Assos J* 2012;6:465-470.
7. 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;94:1458-1468.
8. Lee RJ, Saylor PJ, Smith MR. Treatment and prevention of bone complications from prostate cancer. *Bone* 2011;48:88-95.
9. Logothetis CJ, Lin S-H. Osteoblasts in prostate cancer metastasis to bone. *Nat Rev Cancer* 2005;5:21-28.
10. Gilligan T, Kantoff PW. Chemotherapy for prostate. *Urol* 2002;60:94-100.
11. Pezaro C, Omlin A, Lorente D, de Bono J. Management of patients with castration-resistant disease. *Hematol Oncol Clin North Am* 2013;27:1243-1260.
12. Gkialas IK, Fragkoulis C. Emerging therapies targeting castration-resistant prostate cancer. *J BUON* 2015;20:1389-1396.
13. 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;96:879-882.
14. 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 of Onc* 2012;23:1341-1347.
15. Bamias A, Kastiris E, Bamia C et al. Osteonecrosis of the Jaw in Cancer After Treatment With Bisphosphonates: Incidence and Risk Factors. *J Clin Oncol* 2005;23:8580-8587.
16. Kostenuik PJ, Nguyen HQ, McCabe et al. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock in mice that express chimeric (murine/human) RANKL. *J Bone Miner Res* 2009;24:182-195.
17. Wada T, Nakashima T, Hiroshi N et al. RANKL-RANK signaling in osteoclastogenesis and bone disease. *Trends Mol Med* 2006;12:17-25.
18. 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 randomized, double blind study. *Lancet* 2011;377:813-822.
19. Smith MR, Coleman RE, Klotz L et al. Denosumab for the prevention of skeletal complications in metastatic castration resistant prostate cancer: comparison of skeletal related events and symptomatic skeletal events. *Ann Oncol* 2015;26:368-374.
20. 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.
21. Smith MR, Saad F, Oudard S et al. Denosumab and bone metastasis free survival in men with nonmetastatic castration resistant prostate cancer: exploratory analyses by baseline prostate specific antigen doubling time. *J Clin Oncol* 2013;30:3800-3806.
22. Stopeck AT, Fizazi K, Body JJ et al. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. *Support Care Cancer* 2015 [Epub ahead of print] doi: 10.1007/s00520-015-2904-5.
23. Todenhöfer T, Stenzl A, Hofbauer LC et al. Targeting Bone Metabolism in Patients with Advanced Prostate Cancer: Current Options and Controversies. *Int J Endocrinol* 2015:9.
24. Kinoshita Y, Arai M, Ito N et al. High serum ALP level is associated with increased risk of denosumab-related hypocalcemia in patients with bone metastases from solid tumors. *Endocrinol J* 2016;63:479-484.
25. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213-223.
26. Bruland OS, Nilsson S, Fisher DR et al. High-linear energy transfer irradiation targeted to skeletal metastases by the alpha-emitter ²²³Ra: adjuvant or alternative to conventional modalities? *Clin Cancer Res* 2006;12:6250-6257.
27. Nilsson S, Cislo P, Sartor O et al. Patient-reported quality of life analysis of radium-223 dichloride from the phase 3 ALSYMPCA study. *Ann Oncol* 2016;27:868-874.
28. Morris MJ, Hammers HJ, Sweeney C et al. Safety of radium-223 dichloride (Ra-223) with docetaxel (D) in patients with bone metastases from castration-resistant prostate cancer (CRPC): a phase I prostate cancer clinical trials consortium study. *J Clin Oncol* 2013;31:5021.
29. Saad F. Radium-223 in an international early access program (EAP): effects of concomitant medication on overall survival in metastatic castration-resistant prostate cancer (mCRCP) patients. *J Clin Oncol* 2015;33:5034.
30. Carrasquillo JA, O'Donoghue JA, Pandit-Taskar N et al. Phase I pharmacokinetic and biodistribution study with escalating doses of ²²³Ra-dichloride in men with castration-resistant metastatic prostate cancer. *Eur J Nucl Med Mol Imaging* 2013;40:1384-1393.