Expert Opinion on Biological Therapy

ISSN: 1471-2598 (Print) 1744-7682 (Online) Journal homepage: informahealthcare.com/journals/iebt20

Denosumab as a promising novel bone-targeted agent in castration resistant prostate cancer

Athanasios Dellis & Athanasios G Papatsoris

To cite this article: Athanasios Dellis & Athanasios G Papatsoris (2014) Denosumab as a promising novel bone-targeted agent in castration resistant prostate cancer, Expert Opinion on Biological Therapy, 14:1, 7-10, DOI: 10.1517/14712598.2013.840582

To link to this article: https://doi.org/10.1517/14712598.2013.840582

EXPERT OPINION

Denosumab as a promising novel bone-targeted agent in castration resistant prostate cancer

Athanasios Dellis & Athanasios G Papatsoris[†]
[†]*University of Athens, Sismanoglio General Hospital, School of Medicine, 2nd Department of Urology, Athens, Greece*

Fortunately, more therapeutic progress has been achieved during the last 3 years for patients with castration resistant prostate cancer (CRPC) than during the previous 30 years. During this limited time frame, six compounds (sipuleucel-T, cabazitaxel, denosumab, abiraterone, radium-223 and enzalutamide, listed in chronologic order) yielded positive results in Phase III trials (Fizazi K. Nonhormone therapy for metastatic castration-resistant prostate cancer. Soc Clin Oncol Educ Book 2013;2013:161-5; Papatsoris AG, Karamouzis MV, Papavassiliou AG. Novel biological agents for the treatment of hormone-refractory prostate cancer (HRPC). Curr Med Chem 2005;12(3):277-96). Regarding skeletal related event (SREs) in patients with CRPC the last 20 years bisphosphonates (i.e., zolendronic acid) were the standard of care until the development of denosumab, which is a novel receptor-activated nuclear factor kappa-β ligand inhibitor. Recent studies demonstrated that denosumab (subcutaneous use) was better than zolendronic acid (intravenous use) for the prevention of SREs and the increase of the bone-metastasis-free survival, while the rate and grade of adverse effects was similar, except for osteonecrosis of the jaw and hypocalcemia. Cost-effectiveness of denosumab is under review in ongoing comparative studies.

Keywords: castration, denosumab, prostate cancer, skeletal metastases

Expert Opin. Biol. Ther. (2014) ***14****(1):7-10*

1. Introduction

Prostate cancer (PCa) relapse after hormonal ablation therapy has been identified with several terms including hormone-refractoryPCa, androgen-independent PCa and hormone-independent PCa [1,2]. Nowadays, the term castration resistant PCa (CRPC) is more frequently used based on finding demonstrating that advanced Pca is not uniformly refractory to further hormonal manipulations and that disease progression may be dependent on androgen receptor interactions [3]. Therefore, CRPC is still hormone sensitive and is characterized by three consecutive rises of PSA despite standard hormone manipulations, castration levels of testosterone and anti-androgen withdrawal. In CRPC bone metastases are often present posing a substantial health and economic burden because they induce skeletal-related events (SREs: pathological fractures, spinal cord compression, need for radiotherapy or surgery to the bone).

Prevention of bone metastases and SREs represents a crucial unmet medical need as they increase the risk of death [3]. For the last two decades only intravenous (IV) bisphosphonate zolendronic 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-β ligand: RANKL) has gained Food & Drug Administration (FDA) approval for prevention of SREs in patients with

informa healthcare

10.1517/14712598.2013.840582 © 2014 Informa UK, Ltd. ISSN 1471-2598, e-ISSN 1744-7682

bone metastases from solid tumors and for increasing bone mass in patients with non-metastatic Pca under androgen deprivation therapy (ADT) [4]. Furthermore, although initial ADT is uniformly effective, nearly all patients with eventually develop CRPC with bone metastases, thus the development of novel bone-targeted agents such as denosumab is more than welcomed.

2. Denosumab's mechanisms of action

In the bone microenvironment, growth factors (GFs) secreted by tumor cells induce stromal cells and osteoblasts to express cytokine RANKL, which activates the RANK receptor present on osteoclast precursors and as a result active osteoclasts are produced [5]. Denosumab prevents the interaction of tumor necrosis factor ligand superfamily member 11 (RANKL) with the tumor necrosis factor receptor superfamily member 11A (osteoclast differentiation factor receptor, ODFR/RANK) [6]. This activated signaling pathway is important for the formation, function and survival of osteoclasts [5]. Furthermore, RANKL acts as a tumor cell mediator with marrow stromal cells favoring RANKL production. Bone resorption releases GFs from the bone matrix that perpetuate tumor activity. This vicious cycle results in continuous osteoclast activation and bone destruction process. Denosunab binds to RANKL and prevents the maturation of osteoclasts, decreases bone resorption and breaks the vicious cycle of bone destruction.

In preclinical models with established bone metastases, inhibition of RANKL with denosumab prevented osteoclast-mediated bone destruction and growth of human breast cancer cells in the bone [7]. These studies encouraged researchers to study the use of denosumab in bone remodeling in cases of bone metastases from several solid tumors such as PCa. Furthermore, denosumab is easily administered subcutaneously and it has been developed as two products with different dosing regimens and therapeutic indications. In the dose of 60 mg SC, twice yearly, it is indicated for the treatment of bone loss associated with ADT in men with PCa at increased risk of bone fracture as well as for the treatment of osteoporosis in postmenopausal women at increased risk of fractures. In the dose of 120 mg SC, every month, it is indicated for the prevention of SREs in patients with bone metastases from solid tumors [4].

3. Safety issues

In general, studies have demonstrated that denosumab is well tolerated [8]. Minor adverse effects include anemia, back or bone pain, symptoms from gastrointestinal tract and/or fatigue. Denosumab-associated risk of hypocalcemia is higher in patients with renal insufficiency. In most cases, hypocalcemia is asymptomatic; however, a few fatal cases of hypocalcemia have been reported, highlighting the critical need for adequate supplementation with calcium and vitamin D [8]. Osteonecrosis of the jaw (ONJ) is a serious adverse effect of denosumab administration [9]. 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 [10]. Risk factors for ONJ include the use of a dental appliance, history of tooth extraction and less frequently poor oral hygiene [11]. 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 [9]. 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 [12]. 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.

Lastly, like other monoclonal antibodies the clearance of denosumab is through the reticuloendothelial system and not through the kidney [8]. This is of utmost importance in men with CRPC as they are usually elderly patients with a degree of renal impairment due to obstructive uropathy, other systemic diseases and/or nephrotoxic medication [9].

4. Denosumab in patients receiving ADT

In metastatic PCa, ADT (bilateral orchidectomy, gonadotropin-releasing hormone agonists or antagonists) has been the standard first-line therapy for several decades. However, ADT increases bone resorption, reduces bone mineral density and increases the risk of fracture. Furthermore, the incidence of SREs increases with increasing duration of ADT. In a double-blind, multicenter study, patients receiving ADT for non-metastatic PCa were randomly assigned to receive denosumab (60 mg) or placebo (734 patients in each group) [13]. At 24 months, bone mineral density had increased by 5.6% in the denosumab group compared with a loss of 1% in the control group ($p < 0.001$). These significant differences between the two groups were seen as early as 1 month and were sustained through 36 months. Furthermore, patients that received denosumab had a decreased incidence ($p = 0.006$) of new vertebral fractures at 36 months (6 months after the last dose of the study drug). Rates of adverse effects were similar between the denosumab and the placebo group.

5. Does denosumab affect bone-metastasis-free survival?

Last year, the results of a large randomized study on 1432 men with non-metastatic PCa that received denosumab versus placebo were published [14]. 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 (symptomatic or asymptomatic) 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%) and ONJ (5 vs 0%). These results have been confirmed by other studies and a recent metaanalysis of six controlled studies including 6142 patients [15].

Alpha emitter radium-223 which selectively targets bone metastases with alpha particles has recently been assessed regarding the survival of patients with CRPC [16]. In a Phase III, randomized, double-blind, placebo-controlled study, 921 with CRPC and bone metastases were included. The study found that radium-223 (six IV injections of 50 kBq/kg) significantly prolonged overall survival (by 3.6 months), with a 30% reduction in the risk of death. The highly targeted nature of radium-223, with alpha particles of short range, minimizes myelosuppresion and has limited effects on normal tissue. A comparative study between this novel bone-targeted agent and denosumab would be very interesting.

6. Denosumab versus zoledronic acid in CRPC

A Phase III study conducted by 342 centers compared denosumab (120 mg SC) with zolendronic acid (4 mg IV) for the prevention of SREs in 1904 men with bone metastases from CRPC [17]. Median time to first SRE was 20.7 months with denosumab and 17.1 months with zolendronic acid. The rate and grade of adverse effects was similar between the two groups (including ONJ). More events of hypocalcemia occurred in the denosumab group in comparison with the zolendronicacid group (13 vs 6%; $p < 0.001$). Furthermore, bone resorption markers such as urinary N-telopeptide were found to be significantly suppressed in the denosumab arm compared with the zolendronic acid arm ($p < 0.0001$). The authors concluded that denosumab was better than zolendronic acid for the prevention and delay of SREs in patients with bone metastases from CRPC. Recently, patient-level data from three identically designed, randomized, double-blind, active-controlled, Phase III trials of patients with breast cancer, PCa, other solid tumours or multiple myeloma were combined [18]. Denosumab was superior to zoledronic acid in delaying time to first on-study SRE by a median 8.2 1 months, reducing the risk of a first SRE by 17% ($p < 0.001$). Hypocalcaemia was more common for denosumab, while ONJ occurred at a similar rate ($p = 0.13$).

Alike denosumab, the use of zolendronic acid has 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. These 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. Surprisingly, although bisphosphonates have been used as the standard bone targeted agent in CRPC for many years, the best dosing interval is still unclear and it more frequent (usually every 4 weeks) in comparison with denosumab [4]. Furthermore, the advantages of denosumab over other bisphophonates such as pamidronate and bandronate have been established in similar comparative studies [19].

A very recent systematic review of the clinical effectiveness and cost-effectiveness of denosumab for the treatment of bone metastases compared denosumab with zoledronic acid and placebo [20]. The study demonstrated that denosumab was effective in delaying SREs, but it was similar with regard to quality of life and pain. With the availability of the patient access scheme, denosumab was estimated to be cost-effective relative to zoledronic acid but not to best supportive care. Lastly, another recent study assessed the cost-effectiveness of denosumabvszoledronic acid in bone-metastatic CRPC including the parameter of, quality-adjusted life-years (QALYs) [21]. Denosumab resulted in fewer estimated SREs (-0.241), more QALYs (0.0074) and lower SRE-related costs (-$2340), but higher drug-related costs ($10,181) and total costs ($7841) versus zoledronic acid. The base case estimated cost per QALY-gained was $1,058,741.

7. Epilogue

The tissue tropism of PCa for bone coupled with the skeletal-related adverse effects of ADT has led to heightened awareness of SREs in CRPC. In the European Association of Urology (EAU) updated (2013) guidelines on the management of CRPC the grade of recommendation is 'A' for offering bone protective agents to patients with bone metastases (denosumab being superior to zolendronic acid) [22]. The results of larger ongoing studies that assess the efficacy, safety and cost-effectiveness of denosumab are warranted.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

1. Fizazi K. Nonhormone therapy for metastatic castration-resistant prostate cancer. Soc Clin Oncol Educ Book 2013;2013:161-5
2. Papatsoris AG, Karamouzis MV, Papavassiliou AG. Novel biological agents for the treatment of hormone-refractory prostate cancer (HRPC). Curr Med Chem 2005;12(3):277-96
3. Smith MR, Cook R, Lee KA, Nelson JB. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant non-metastatic prostate cancer. Cancer 2011;117(10):2077-85
4. Heidenreich A, Bastian PJ, Bellmunt J, et al. Guidelines on prostate cancer. In European Association of Urology (EAU) Guidelines, edition presented at the 28th Annual EAU Congress, Milan; 2013
5. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature 2003;423(6937):337-42
6. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011;48(4):677-92
7. Canon JR, Roudier M, Bryant R, et al. Inhibition of RANKL blocks skeletal tumor progression and improves survival in a mouse model of breast cancer bone metastasis. Clin Exp Metastasis 2008;25(2):119-29
8. Gartrell BA, Coleman RE, Fizazi K, et al. Toxicities following treatment with bisphosphonates and receptor activator of nuclear factor-κB ligand inhibitors in patients with advanced prostate cancer. Eur Urol 2013; Epub ahead of print
9. Qi WX, Tang LN, He AN, et al. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. Int J Clin Oncol 2013; Epub ahead of print
10. Pazianas M. Osteonecrosis of the jaw and the role of macrophages. J Natl Cancer Inst 2010;103:232-40
11. Vahtsevanos K, Kyrgidis A, Verrou E, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J Clin Oncol 2009;27(32):5356-62
12. van Poznak CH, Temin S, Yee GC, et al. ASCO Clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. JCO 2001;29(9):1221-7
13. 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(8):745-55
14. Smith MR, Saad F, Coleman R, et al. Denosumab and bone metastasis-free survival in men with castration-resistant prostate cancer: results of a global phase 3, randomised, placebo-controlled trial. Lancet 2012;379(9810):39-46
15. Peddi P, Lopez-Olivo MA, Pratt GF, Suarez-Almazor ME. Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis. Cancer Treat.Rev 2013;39(1):97-104
16. Parker C, Nilsson S, Heinrich D, et al. Alpha Emiter Radium-223 and survival in metastatic prostate cancer. NEJM 2013;369(3):213-23
17. 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(9768):813-22
18. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer 2012;48(16):3082-92
19. Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor-kappa B ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res 2006;12(4):1221-18
20. Ford J, Cummins E, Sharma P, et al. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. Health Technol Assess 2013;17(29):1-386
21. Snedecor SJ, Carter JA, Kaura S, Botteman MF. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a cost-effectivenessanalysis. J Med Econ 2013;16(1):19-29
22. Heidenreich A, Bastian PJ, Bellmunt J, et al. Guidelines on prostate cancer. In European Association of Urology (EAU) Guidelines, edition presented at the 28th EAU Annual Congress, Milan; 2013

Affiliation

Athanasios Dellis[1,2] &
Athanasios G Papatsoris[†1,3,4]
[†]Author for correspondence
[1]University of Athens,
Sismanoglio General Hospital,
School of Medicine, 2nd Department of Urology,
Athens 15126, Greece
E-mail: agpapatsoris@yahoo.gr
[2]University of Athens, Areteion Hospital,
School of Medicine, 2nd Department of Surgery,
Athens 11528, Greece
[3]Hellenic Genito-Urinary Cancer Group,
Athens 11527, Greece
[4]Institute of Molecular Medicine &
Biomedical Research, Athens 10678, Greece