EXPERT OPINION

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Molecular target therapy for bone metastasis: starting a new era with denosumab, a RANKL inhibitor

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Introduction: The skeleton is generally the primary, and sometimes the only, site of metastasis in patients with advanced solid tumors. Bone metastases are the most frequent cause of cancer-related pain and the origin of severe morbidity in patients. Among the treatment options available for the prevention of skeletal-related events (SREs) associated with bone metastasis, zoledronic acid, an antiresorptive treatment from the group of bisphosphonates, is currently the standard of care in this setting.

Areas covered: Zoledronic acid, together with denosumab (a monoclonal antibody against the receptor activator of nuclear factor kappa B ligand), is the most frequent approach for the prevention of cancer-related events in skeleton. This paper reviews several trials evaluating the efficacy of denosumab in comparison with zoledronic acid in patients with solid osteotropic tumors. In this setting of skeleton-invading cancers, denosumab was demonstrated to be superior to zoledronic acid in preventing or delaying SREs. In comparison with zoledronic acid, denosumab significantly delayed the time to first SRE by 17%.

Expert opinion: Current research on denosumab is addressed to prove the immunomodulator effect of this agent in humans. Other avenue of research is focused on its antitumor activity observed in some Phase III trials.

Keywords: bone metastasis, breast cancer, denosumab, prostate cancer, skeletal-related events, solid tumors

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1. Introduction

Bone metastases are a complication in a wide range of malignancies. The skeleton is a frequent site of metastases, with it generally being the first, and sometimes the only, site in patients with osteotropic advanced tumors. Bone metastases cause considerable morbidity. It is well known that some types of tumors present a more predictable pattern of spread than others. Tumors associated with skeletal metastases and bone loss are mainly prostate cancer, breast cancer and multiple myeloma. Metastases to the bone may produce fractures, hypercalcemia, pain and a decrease in the mobility and performance status of the patient [1].

Skeletal metastases are usually divided into osteolytic lesions, in which the resorption of the normal bone is the predominant process, and osteoblastic lesions, in which the predominant process includes the deposition of new bone. However, this division is not absolute and many lesions may result from a mixed process. In patients with breast cancer as well as in patients with multiple myeloma, bone

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Article highlights.

- To date, zoledronic acid has represented the most important tool to reduce the risk of SREs in patients with bone metastases.
- Denosumab targets the RANKL pathway, which is essential for the activation of bone resorption by osteoclasts.
- Denosumab provided an alternative to bisphosphonates for control of bone metastases-related events.
- Denosumab has been studied in various solid tumors, including breast cancer and prostate cancer.
- The advantages of denosumab over bisphosphonates are with regard to both the efficacy in term of delayed time to first SRE and in reduced rates of acute phase reactions and renal adverse effects.
- Interesting findings about denosumab with regard to the potential immunomodulatory effects and antitumor activity are suggested.

This box summarizes key points contained in the article.

metastases are predominantly osteolytic lesions, whereas osteoblastic lesions are commonly detected in patients with prostate cancer [2-5].

Bone loss in cancer patients is a multifactorial process. The understanding of the pathophysiological mechanisms involved in this process has provided new approaches to these events. One important emerging therapy includes, as part of its mechanism, the blocking of the receptor activator of nuclear factor kappa B (NF-κB) ligand (RANKL) to its natural receptor (RANK). This inhibits osteoclastogenesis and, thus, reduces bone resorption and interferes with mechanisms that stimulate osteoblastic bone formation, while inhibiting osteoclastic resorption [6].

2. Incidence and consequences of bone metastasis

The prevalence of bone metastasis in cancer patients is particularly high. Skeletal metastases are detected in 65 – 75% of patients with advanced prostate cancer and this percentage is even higher in patients who eventually die from the disease. The issue may become even worse due to the fact that the administration of androgen deprivation therapy for advanced prostate cancer promotes bone loss and therefore, skeletal-related events (SREs) [7]. SREs are defined as pathological fractures, spinal cord compression and radiotherapy for bone and bone surgery and are associated with increased morbidity and mortality in patients with bone metastases. Bone metastases are also present in ~ 65 – 75% of advanced breast cancer patients [8]. As in patients with prostate cancer, bone loss in breast cancer patients is the result of cancer and its treatment. As an example, aromatase inhibitors, which are drugs commonly used for the treatment of estrogen receptor-positive breast cancer, are agents that increase the risk of osteoporosis [9,10]. In addition, breast cancer is most likely to affect postmenopausal women. In these patients, there is an additional high age- and gender-related risk for bone loss and fracture associated with the estrogen decline, which is even more pronounced due to the administration of aromatase inhibitors to these patients [11]. Moreover, women with chemotherapy-induced ovarian failure have an increased risk for osteoporosis. **Table 1** shows the incidence of bone metastasis by tumor type.

The normal mechanism of bone metabolism in patients with cancer can be significantly disrupted by treatment and metastasis. Both events especially alter the process of osteoclastic bone resorption. There are at least four factors driving the development of bone metastases: cancer cells, osteoblasts, osteoclasts and mineralized bone matrix, which releases growth factors. However, the main characteristic of all metastatic bone lesions is the deregulated increase of bone resorption by osteoclasts in a process similar to that leading to osteoporosis. Malignant lesions in bone are, thus, classified as i) osteolytic, when the main process is bone destruction; ii) osteoblastic, when the predominant process is the formation of new, weaker bone; or iii) mixed lesions. The incidence of pathological fractures is higher in osteolytic lesions [12,13].

The median survival for patients from the time of diagnosis of bone metastasis varies among different tumor types. In the case of breast and prostate cancer, survival is measured in years. In contrast, in the case of lung cancer, the survival from the time of diagnosis of bone metastasis is measured in months (**Table 1**) [14,15]. Nevertheless, coexisting nonosseous metastases are also important in prognosis. Thus, in patients with advanced breast cancer who present a first relapse to the bone, the probability of survival is influenced by the subsequent development of extraosseous metastases [16,17].

Skeletal metastasis is the cause of severe morbidity in patients with advanced cancer. Pain, hypercalcemia, pathological bone fractures, neurological deficits due to the compression of nerves by the collapse of vertebrae and reduced activity associated with bone metastases all lower a patient's quality of life [18]. A patient with bone metastatic disease experiences, on average, a SRE every 3 – 6 months. The occurrence of these events is not regular but becomes more frequent as the disease becomes more extensive [19].

Common sites of bone metastases associated with pain are the base of skull, vertebrae, pelvis and femur. Hypercalcemia had been frequently detected in patients with cancer and bone metastases; however, this symptom has become a rare event since the advent of antiresorptive therapy to treat bone metastases [20]. Hypercalcemia is the result of the bone destruction characteristic of osteolytic metastases. Secretion of humoral and paracrine factors by tumor cells increases osteoclast activity and proliferation as well as the production of markers of bone turnover [21,22]. It is likely that tumor cells exploit the same molecules to induce proliferation and activate osteoclasts to favor the implantation of metastatic cells and their spread in bone tissue. The osteoclastogenic factors produced by tumor cells include parathyroid hormone-related

Table 1. Incidence of bone metastasis according to tumor type and median survival [6,8].

Tumor type	Incidence of bone metastasis (%)	Median survival from diagnosis of bone metastasis (months)
Multiple myeloma	90 – 100	NR
Prostate cancer	65 – 75	12 – 53
Breast cancer	65 – 75	19 – 25
Bladder cancer	40	6 – 9
Lung cancer	30 – 40	6 – 7
Kidney cancer	20 – 25	12
Thyroid cancer	60	48

NR: Not reported.

protein (PTHrP) and RANKL. In addition, the kidney may be involved in the development of malignant hypercalcemia, due to volume depletion. Moreover, the action of parathyroid hormone-related peptide increases the reabsorption of calcium, thus further elevating the serum calcium levels. Left untreated, hypercalcemia results in the deterioration of renal function and of the mental status of the patient, and death may result from cardiac arrhythmias and renal failure.

With regard to pathological bone fractures, the destruction of bone primarily results in microfractures, which leads to chronic pain in patients. Subsequently, long bone fractures may occur, causing a higher grade of disability, while the compression of the spinal cord is another SRE associated with bone metastases. Radiation is an effective therapy for metastatic bone disease. This therapy not only diminishes tumor mass and promotes bone healing of osteolytic lesions but also leads to pain relief. Pain is thought to be relieved as a secondary mechanism to tumor shrinkage and also due to the inhibition of chemical pain mediators [23]. Spinal cord compression constitutes a severe medical emergency. Pain, in this case, is frequently localized in the area of the tumor and the radicular pain gets worse at night. However, it may also radiate down a limb or around the chest or abdomen. The majority of patients presenting spinal cord compression describe weakness, paralysis, numbness, distal anesthesia, urinary retention, incontinence and impotence. However, if the lesion occurs in the *conus medullaris*, patients may present dysfunction of the bladder, rectum and genitalia. With regard to spinal instability, this event occurs in 10% of the patients with advanced cancer who present back pain. Surgery is often required in order to relieve such pain [19].

3. Prevention of SREs in patients with advanced cancer

Among the treatment options available for the prevention of SREs associated with bone metastases, bisphosphonates, such as zoledronic acid, are one of the therapeutic groups that are more extensively used in this setting. Denosumab, a monoclonal antibody, exerts its efficacy through the suppression of osteoclast formation via a mechanism of action different from that exploited by bisphosphonates.

3.1 Role of bisphosphonates

Currently, it is well known that bisphosphonates can reduce bone pain, alongside the use of analgesics and bone irradiation, and are a reliable solution for the underlying cause of SREs and malignant osteolysis, delaying the onset and reducing the incidence of these events [24-26]. There are two types of bisphosphonates with different mechanisms of action [27]. Bisphosphonates are preferentially incorporated into sites of active bone remodeling. They inhibit hydroxyapatite breakdown with subsequent effective suppression of bone resorption. Bisphosphonates also function to limit both osteoblast and osteocyte apoptosis. The first type is non-nitrogen-containing bisphosphonates, such as clodronate, which are metabolized into cytotoxic compounds by osteoclasts and the second type is nitrogen-containing bisphosphonates. This group includes zoledronic acid, pamidronate and ibandronate, which inhibit the mevalonate pathway, leading to osteoclast apoptosis. Both types of bisphosphonates may be administered for the prevention and treatment of SREs associated with bone metastases in cancer patients.

At the present time, zoledronic acid is considered the current standard of care for preventing or delaying SREs in cancer patients who have bone metastases [28].

3.2 Role of denosumab

Denosumab is a fully monoclonal antibody that binds and neutralizes RANKL. Through this binding, denosumab inhibits osteoclast function as well as bone resorption and local bone destruction.

3.2.1 Preclinical data and mechanism of action of denosumab

Tumor necrosis factor (TNF) receptor superfamily member 11B, also known as osteoprotegerin (OPG), is a decoy factor for RANKL. By its union with RANKL, OPG inhibits NF-κB, which is crucial for cell survival and differentiation. The significance of the RANKL/RANK pathway has been demonstrated in knockout experiments in which either $RANK^{-/-}$ or $RANKL^{-/-}$ mice presented important defects in bone resorption, lymph node formation and B-cell development [29]. In contrast, $OPG^{-/-}$ mice developed osteoporosis and hypercalcemia, according to the results of another study [30]. Thus, the balance between RANKL and its receptor RANK, as well as its decoy factor OPG, is essential for bone and calcium homeostasis. Not unexpectedly, this balance is shifted toward bone resorption in several human diseases, such as cancer.

Denosumab has been produced in transgenic mice by the deletion and replacement of their murine immunoglobulin genes with human orthologs [31]. As both OPG and denosumab have a similar mechanism of action, OPG has been

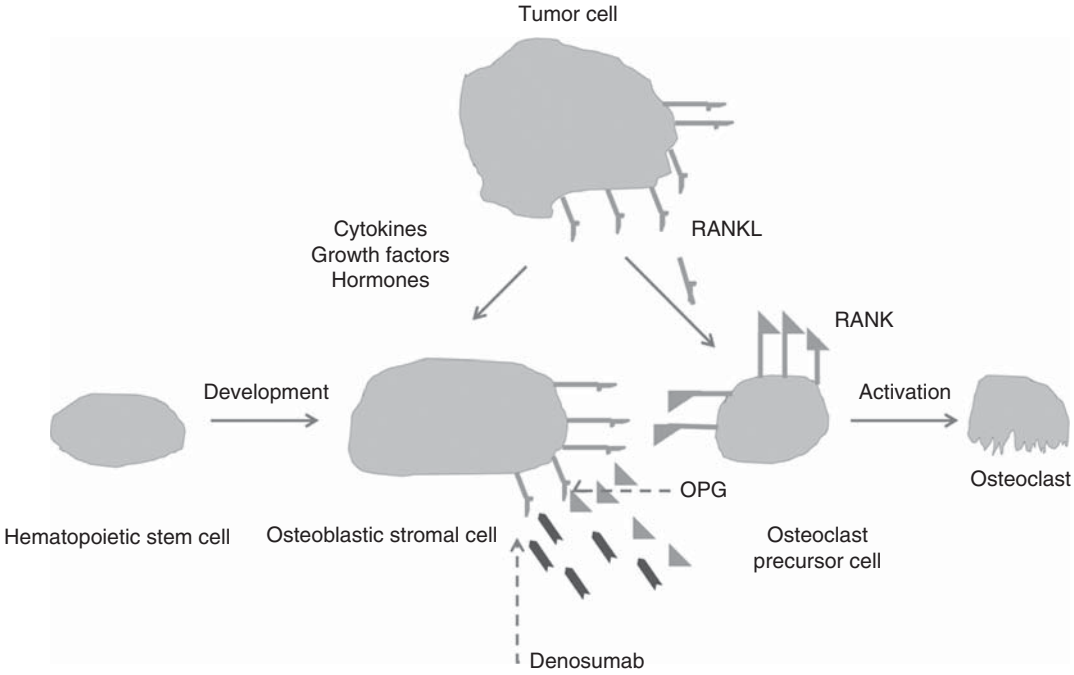

Figure 1. Illustration of mechanism of action of denosumab.
Dashed lines: Inhibition routes; OPG: Osteoprotegerin; RANK: Receptor activator of nuclear factor kappa B; RANKL: RANK ligand.

used as a surrogate for the study of RANKL inhibition in animal models. Through these tests, it was demonstrated that OPG importantly reduces the amount of osteoclasts in bone lesions arising from direct intratibial infection of cancer cells from human prostate cancer in immunodeficient mice [32]. Experiments in rats have demonstrated that a single injection of OPG results in a rapid, sharp reduction in the proportion of bone surfaces occupied by osteoclasts, that is, a 95% reduction within 12 h after its administration. This reduction gradually returned to normal values from days 10 to 30 after the injection.

However, denosumab has several differences in terms of selectivity over OPG. Denosumab does not bind to TNF-related apoptosis-inducing ligand (TRAIL) or other TNF family members, such as TNF-α, TNF-β and CD40 ligand, whereas TRAIL binding has been observed with OPG [33,34].

Denosumab targets the RANKL pathway. This pathway is essential for osteoclast differentiation, activation and function and its expression is thought to be induced by products of cancer cells, such as the PTHrP [35].

Figure 1 shows the role of RANKL, the receptor RANK and the decoy factor OPG in the control of bone metabolism and the mechanism of action of denosumab. In bone lytic lesions related to cancer, this balance is shifted in favor of RANKL expression and the decrease in OPG expression. Generally, cancer cells upregulate RANKL expression on stromal osteoblasts by the secretion of regulatory cytokines and hormones. In some instances, cancer cells can express RANKL and directly activate osteoclasts [32,36].

RANKL is expressed not only by osteoblasts but also by activated T cells and synoviocytes [37]. RANK is a receptor expressed by monocytes, macrophages and dendritic cells. The RANK–RANKL interaction has been demonstrated to be involved in immunomodulation in different animal models [38]. RANKL is expressed on a number of T and B cells, and $CD4^+CD25^+$ T cells have been shown to be regulated by the RANK–RANKL signaling system. Denosumab, as an inhibitor of the RANK–RANKL signaling, has the potential to be an immunomodulator. Studies with mouse keratinocytes suggest that blocking RANKL in mice decreases the number of regulatory T cells in skin, thus leading to an increased inflammatory response.

3.2.2 Efficacy data of denosumab

In **Table 2**, the main efficacy data of denosumab in comparison with zoledronic acid from randomized trials is summarized.

3.2.2.1 In advanced breast cancer

A randomized, double-blind study was conducted by Stopeck *et al.* to test the efficacy of denosumab in 2046 patients with advanced breast cancer and metastases to bone [39]. These patients were randomly assigned to receive subcutaneous denosumab (120 mg) plus intravenous placebo or intravenous zoledronic acid (4 mg) plus subcutaneous placebo every 4 weeks. Randomization was stratified by prior SRE, prior oral bisphosphonate use, current chemotherapy and geographical region (Japan or other regions). All patients

Table 2. Main efficacy data of denosumab and zoledronic acid in cancer patients with bone metastasis.

Study	No.	Type of patients	Treatment	Time to first on-study SRE	Time to first and subsequent on-study SREs
Stopeck *et al.* [39]	1026 1020	Advanced breast cancer	Denosumab Zoledronic acid	HR: 0.82; 95% CI: 0.71 – 0.95; p < 0.001 for noninferiority and p = 0.01 for superiority	RR: 0.77; 95% CI: 0.66 – 0.89; p = 0.001, adjusted superiority
Fizazi *et al.* [40]	950 951	Advanced prostate cancer	Denosumab Zoledronic acid	HR: 0.82; 95% CI: 0.71 – 0.95; p = 0.0002 for noninferiority and p = 0.008 for superiority	RR: 0.82; 95% CI: 0.71 – 0.94; p = 0.008 adjusted superiority
Henry *et al.* [41]	886 890	Advanced multiple myeloma or solid tumors, excluding breast and prostate cancer	Denosumab Zoledronic acid	HR: 0.84; 95% CI: 0.71 – 0.98; p = 0.0007 for non-inferiority; for superiority, p = 0.03 unadjusted and p = 0.06 adjusted	RR: 0.90; 95% CI: 0.77 – 1.04; p = 0.14 adjusted superiority

CI: Confidence interval; HR: Hazard ratio; RR: Rate ratio; SRE: Skeletal-related event.

were recommended to take calcium and vitamin D supplements. Denosumab was demonstrated to be superior to zoledronic acid in delaying the time to first on-study SRE (hazard ratio [HR] 0.82; 95% CI: 0.71 – 0.95; p < 0.001 for noninferiority and p = 0.01 for superiority). In addition, denosumab was superior to zoledronic acid in the time to first and subsequent on-study SREs, with a rate ratio of 0.77 (95% CI: 0.66 – 0.89; p = 0.001 for superiority). Additionally, bone turnover marker levels showed a greater reduction in the denosumab treatment arm than in the control arm.

Similar values were observed in terms of overall survival (OS), disease progression and adverse event (AE) rates of any grade, as well as in the incidence of severe AEs (SAEs). However, acute phase reactions and renal AEs were more frequent in patients treated with zoledronic acid, whereas hypocalcemia was frequently observed in patients treated with denosumab. With regard to osteonecrosis of the jaw (ONJ), this AE was not differentially observed in any of the study arms, occurring in 2% of the patients in the denosumab arm in comparison with 1.4% of the patients in the zoledronic acid arm (p = 0.39). Hence, denosumab was shown to be superior to zoledronic acid in delaying as well as preventing SREs in patients with advanced breast cancer and metastasis to bone. Denosumab also demonstrated a good safety profile. Unlike patients treated with zoledronic acid, patients treated with denosumab did not require renal monitoring. Denosumab was demonstrated to be superior to zoledronic acid in delaying or preventing SREs in patients with breast cancer and metastasis to bone. This drug was also well tolerated.

3.2.2.2 *In advanced prostate cancer*

The treatment of bone metastases in patients with castration-resistant prostate cancer (CRPC) was tested in a randomized, double-blind, Phase III study [40]. The randomization of 1904 patients was stratified by previous SREs, prostate-specific antigen concentration and chemotherapy for prostate cancer administered within 6 weeks prior to the randomization. Patients were randomized to receive 120 mg of subcutaneous denosumab plus intravenous placebo or 4 mg of intravenous zoledronic acid plus subcutaneous placebo every 4 weeks. All patients were recommended to take supplements of calcium and vitamin D. Median time to first on-study SRE was significantly longer in the denosumab arm (20.7 months) than in the zoledronic acid arm (17.1 months; HR = 0.82; 95% CI: 0.71 – 0.95; p = 0.0002 for noninferiority and p = 0.008 for superiority). In terms of time to first and subsequent on-study SREs, patients treated with denosumab showed 494 SREs in comparison with 584 SREs detected in the zoledronic acid arm. The SREs rate ratio was 0.82 (95% CI: 0.71 – 0.94; p = 0.004 unadjusted and p = 0.008 adjusted for multiplicity).

Thus, 1888 of 1904 patients were included in the safety profile assessment. SAEs were recorded in 63% of the patients treated with denosumab and 60% of the patients treated with zoledronic acid. Some differences between arms were found in the frequency of certain AEs. With regard to hypocalcemia, a higher number of events were observed in patients treated with denosumab compared with those treated with zoledronic acid (13 vs 6%, respectively; p < 0.0001). However, ONJ was not frequent in any of the treatment groups (2 vs 1%, respectively; p = 0.09). Thus, denosumab was superior to zoledronic acid in the prevention of SREs in patients with CRPC and skeleton metastatic disease.

3.2.2.3 *In advanced solid tumors and multiple myeloma*

A randomized, double-blind, Phase III study evaluated the efficacy and safety of denosumab in comparison with zoledronic acid in patients with multiple myeloma or solid tumors, excluding breast and prostate cancer, who presented metastases to the bone [41]. Patients were randomly assigned to receive a subcutaneous injection of denosumab (120 mg)

Table 3. Types of tumors included in the Henry *et al*. trial [41].

Type of tumor	Denosumab, n = 890 n (%)	Zoledronic acid, n = 886 n (%)	All, n = 1776 n (%)
NSCLC	350 (40)	352 (40)	702 (40)
Multiple myeloma	87 (10)	93 (10)	180 (10)
Renal	70 (8)	85 (10)	155 (9)
Small-cell lung cancer	61 (7)	48 (5)	109 (6)
Bladder	28 (3)	35 (4)	63 (4)
Rectal	25 (3)	35 (4)	60 (3)
Colon	30 (3)	29 (3)	59 (3)
Unknown primary	31 (4)	27 (3)	58 (3)
Head and neck	24 (3)	19 (2)	43 (2)
Cervix	18 (2)	25 (3)	43 (2)
Gastric	19 (2)	16 (2)	35 (2)
Non-Hodgkin lymphoma	17 (2)	15 (2)	32 (2)
Soft tissue sarcoma	18 (2)	13 (2)	31 (2)
Endometrial	16 (2)	11 (1)	27 (2)
Other	14 (2)	11 (1)	25 (1)
Esophageal	10 (1)	15 (2)	25 (1)
Neuroendocrine	14 (2)	10 (1)	24 (1)
Carcinoid melanoma	12 (1)	11 (1)	23 (1)
Ovarian	12 (1)	7 (0.8)	19 (1)
Thyroid	7 (0.8)	6 (0.7)	13 (0.7)
Pancreatic	3 (0.3)	8 (0.9)	11 (0.6)
Renal, pelvis and ureter	4 (0.5)	5 (0.6)	9 (0.5)
Gastrointestinal, other	4 (0.5)	4 (0.4)	8 (0.5)
Hodgkin's disease	5 (0.6)	2 (0.2)	7 (0.4)
Liver	1 (0.1)	4 (0.4)	5 (0.3)
Anal	1 (0.1)	2 (0.2)	3 (0.2)
Testicular	2 (0.2)	1 (0.1)	3 (0.2)
Skin, squamous cell	2 (0.2)	0 (0.0)	2 (0.1)
Biliary tract	1 (0.1)	1 (0.1)	2 (0.1)

EPAR: European Public Assessment Report.

plus an intravenous infusion of placebo or an intravenous infusion of zoledronic acid (4 mg) plus a subcutaneous injection of placebo every 4 weeks. Patients were stratified by tumor type, namely non-small-cell lung cancer (NSCLC), multiple myeloma or other type of tumor. A description of the existing primary tumor types in this clinical trial is presented in **Table 3**. Patients with multiple myeloma were limited to 10% of the study population. Daily supplementation of calcium and vitamin D was recommended to every patient. Last, monitoring of creatinine clearance was carried out in patients treated with zoledronic acid.

Denosumab was noninferior to zoledronic acid in delaying the time to first on-study SRE (HR = 0.84; 95% CI: 0.71 – 0.98; p = 0.0007 for noninferiority and p = 0.06 for superiority), resulting in a 16% reduction in this ratio. The median time to first on-study SRE was 20.6 months for denosumab in comparison with 16.2 months for zoledronic acid (p = 0.03 unadjusted and p = 0.06 adjusted for multiplicity). Time to first and subsequent SREs analysis resulted in a rate ratio of 0.90, when denosumab was compared with zoledronic acid (95% CI: 0.77 – 1.04; p = 0.14), which did not achieve statistical significance. OS and disease progression values were similar in both groups of treatment. In an *ad hoc* analysis examining the effect of denosumab relative to zoledronic acid in the subset of patients with multiple myeloma, an assessment in terms of OS demonstrated an HR of 2.26 (95% CI: 1.13 – 4.50); However, denosumab has not been approved for the treatment of patients with multiple myeloma and bone metastases.

However, patients treated with denosumab presented a higher suppression of bone turnover markers than patients treated with zoledronic acid. Between baseline and week 13, urinary N-telopeptides (uNTx):creatinine ratio decreased by 76% in patients treated with denosumab and by 65% in patients treated with zoledronic acid (p < 0.001). Bone-specific alkaline phosphatase decreased by 37% in patients treated with denosumab and by 29% in patients treated with zoledronic acid (p < 0.001). These bone markers have different origin. In particular, NTx is related to osteoclast activity and bone-related alkaline phosphatase is a consequence of osteoblast activation.

In terms of safety profile, both treatment groups experienced similar overall AEs and SAEs (66% in patients treated with zoledronic acid and 63% in patients treated with denosumab). In addition, infectious AE rates were similar: 40 and 41%, respectively. Hypocalcemia occurred as expected at higher frequency in patients treated with denosumab than in those with zoledronic acid (10.8 vs 5.8%), although no clinical consequences were observed in these patients. Regarding ONJ, similar rates were obtained with both treatments as well as similar cumulative incidence rates after 1, 2 or 3 years of treatment (p = 1). Among patients who developed ONJ, risk factors associated with this AE were also observed. These risk factors were present in 91% of patients receiving zoledronic acid and 70% of patients receiving denosumab.

Within the first 3 days after the administration of the first dose, AEs associated with acute phase reactions occurred in 14.5% of the patients treated with zoledronic acid and 6.9% of the patients treated with denosumab. There were no dose adjustments or withholding due to renal function in patients treated with denosumab. In spite of dose adjustments or treatment withholdings in the zoledronic acid arm, renal AEs occurred in 11% of patients treated with zoledronic acid and 8% of patients receiving denosumab. Hence, this new agent was demonstrated to be noninferior, with a trend toward superiority, to zoledronic acid in the prevention or delay of first on-study SRE in patients with advanced solid tumors or multiple myeloma and metastases to bone.

Henry *et al.* also conducted a subanalysis of this trial in 1597 patients with exclusively solid tumors and bone metastasis [42]. In this subanalysis, the delay achieved by denosumab in the time to the first on-study SRE was higher than with zoledronic acid (HR = 0.81; 95% CI: 0.68 – 0.96; p < 0.020). In time to first and subsequent SREs, denosumab showed more favorable result than zoledronic acid

(HR = 0.85; 95% CI: 0.72 – 1; p < 0.05). Results for OS (HR = 0.92; 95% CI: 0.81 – 1.05; p = 0.21) and disease progression (HR = 0.96; 95% CI: 0.85 – 1.08; p = 0.5) were similar in both treatment arms. Regarding the safety profile, although in both arms the incidence of overall AEs was similar, patients treated with zoledronic acid presented a higher rate of AEs potentially associated with renal toxicity (10.3%) than patients treated with denosumab (7.1%). In addition, more acute phase reactions were observed in the zoledronic acid arm (14.8%) than in the denosumab arm (7.1%). In contrast, the incidence of severe (grades 3 or 4) hypocalcemia was more frequently observed with denosumab than with zoledronic acid (4.4 vs 1.8%, respectively). Last, the incidence of ONJ was rarely observed in both treatment arms.

In a recent systematic review with meta-analysis on comparison between denosumab and bisphosphonates, the former had lower incidence of renal toxicity (rate ratio [RR] = 0.76; 95% CI: 0.59 – 0.98) and acute phase reactions (RR = 0.42; 95% CI: 0.37 – 0.49). No differences of CTCAE v4.0 grade 3 AEs, ONJ, new cancers and the incidence of infections were observed between the two kinds of drugs. Denosumab had similar risk to bisphosphonates in the occurrence of ONJ, but an increased trend in the denosumab group was noted (1.8 vs 1.3%, respectively) [43].

3.2.2.4 *Integrated analysis of three Phase III trials*

Three identically designed Phase III pivotal trials were evaluated through a predetermined integrated analysis [44]. The integrated analysis was conducted to assess the delay or the prevention effect of denosumab on SREs in comparison with zoledronic acid in patients with several types of osteotropic cancers. A total of 5723 patients with different diagnoses of cancer such as breast, prostate and other type of solid tumors or multiple myeloma were included, representing 2988 SREs (1360 for denosumab; 1628 for zoledronic acid).

Denosumab was superior to zoledronic acid in delaying the time to first on-study SRE by 17% (median time to first SRE: 27.7 vs 19.5 months: HR = 0.83; 95% CI: 0.76, 0.90; p < 0.0001 both for noninferiority and superiority). In terms of delay of the time to first and subsequent on-study SREs, denosumab was also superior to zoledronic acid by 18% (HR = 0.82; 95% CI: 0.75, 0.89; p < 0.001 for superiority). In both treatment arms, values were similar in terms of overall disease progression (HR = 1.02; 95% CI: 0.95 – 1.08; p = 0.63) and survival (HR = 0.99; 95% CI: 0.91 – 1.07; p = 0.71).

Regarding the safety profile, similar percentages of AEs as well as SAEs were reported in both treatment groups. However, hypocalcemia was reported in 9.6% of patients treated with denosumab and in 5% of patients treated with zoledronic acid. Data regarding ONJ did not differ significantly in both arms (1.8% with denosumab vs 1.3% with zoledronic acid; p = 0.13). Interestingly, ONJ was resolved in 29.7% for zoledronic acid and 40.4% for denosumab. Regarding hypocalcemia, this AE was reported in 9.6% of patients treated with denosumab and 5% of patients treated with zoledronic acid. AEs related to renal toxicity had 2.6% higher incidence in patients treated with zoledronic acid than in those treated with denosumab. Finally, AEs related with acute phase reactions to the drug were reported by 8.7 vs 20.2% of patients treated with denosumab and zoledronic acid, respectively. Hence, denosumab was superior to zoledronic acid in delaying or preventing SREs in a wide range of cancer types with bone metastases.

In another integrated analysis of the three pivotal trials carried out by Cleeland *et al.*, patients completed the Brief Pain Inventory (range: 0 – 10) and several evaluations of pain severity were carried out throughout the analysis. Time to clinically significant pain worsening was delayed in patients treated with denosumab in comparison with patients treated with zoledronic acid (181 vs 169 days, respectively; HR = 0.92; 95% CI: 0.86 – 0.99; p = 0.026). Patients treated with denosumab, with no pain or with mild pain at baseline, showed a more prolonged time to moderate or severe pain in comparison with patients treated with zoledronic acid (p = 0.0002). Time to pain improvement was similar in both groups of patients (p = 0.844). Hence, denosumab prevents clinically relevant increase in pain in comparison with zoledronic acid in all the tumor types tested. In addition, denosumab was similar in terms of pain relief to zoledronic acid [45].

3.3 Other treatments of SREs in patients with advanced cancer

The pharmacological approach for the treatment of painful osseous metastases follows the World Health Organization analgesic stepladder guidelines to pain relief [46,47]. Analgesic agents that may play a role in this approach include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, antidepressants, anticonvulsants, muscle relaxants, α-2 adrenergic agonists, *n*-methyl-d-aspartate receptor antagonists and opioids or opioid-like analgesic agents. The use of traditional, non-selective NSAIDs in cancer-related bone pain is under scrutiny due to lack of robust evidence about their ability to relieve pain in metastatic bone disease. However, COX-2 inhibitors may be of greater therapeutic potential, partially due to their antiangiogenic properties [48,49]. With regard to opioid analgesics, while long-acting opioids are administered for constant or baseline pain, rapid-onset opioids address breakthrough pain, characteristic of advanced bone metastases. An inconvenience with the use of opioids is that this type of drug may be overused, abused or misused in chronic cancer [50]. An anticonvulsant, gabapentin, has been demonstrated to be useful in the treatment of neuropathic cancer pain [51], as well as having adjuvant properties, synergistic with opioid analgesics [52].

The administration of external beam radiotherapy induces the removal of cancer cells from the bone and facilitates the

repair of the bone with osteoblasts [53]. External beam radiotherapy may lead to improvements in analgesia as well as to functional improvements and reduction of the risk of bone fracture. It has been demonstrated that 80% of patients receiving radiotherapy to the bone experience partial or complete pain relief within 10 – 14 days after the initiation of therapy [54]. On the other hand, radiopharmaceutical therapy is an approach which provides several advantages over conventional external beam radiotherapy, such as i) intravenous administration; ii) usefulness in the treatment of multiple, diffuse sites with mild bone marrow depression and iii) fewer AEs associated with the administration of radiopharmaceuticals in comparison with radiotherapy [55]. The experimental radiopharmaceutical radium-223 chloride, also named alpharadin, is a new type of targeted cancer therapy for bone metastases. Alpharadin is under development and is currently being studied for the treatment of patients with advanced prostate cancer and bone metastases via α-radiation [56]. Interventional techniques also give optimal results in patients with painful bone metastases. The most frequently performed techniques for patients with painful bone metastases are vertebral ablation, subdivided into radiofrequency ablation and cryoablation, and vertebral augmentation procedures, which are carried out in patients with spinal metastases and vertebral compression fractures. The most frequent vertebral augmentation procedures are percutaneous vertebroplasty and percutaneous kyphoplasty [57]. Recently the Phase III Alpharadin in Symptomatic Prostate Cancer Patients study compared the efficacy and safety of radium-223 versus placebo in patients with CRPC and bone metastases. It showed an improvement of OS by radium-223 [58].

4. Recommendations issued in treatment guidelines

With regard to breast cancer, the National Comprehensive Cancer Network (NCCN) guidelines have recognized the superiority of denosumab in comparison with zoledronic acid in terms of time to the occurrence of SREs, as a secondary end point of a randomized, active controlled trial [59]. As a result, these guidelines open the way for women with metastatic breast cancer to bone, who are candidates for bisphosphonates therapy, to be considered for treatment with denosumab.

Moreover, the guidelines address recommendations in order to prevent ONJ, such as dental examination prior to treatment with bisphosphonates or denosumab, as well as avoiding dental procedures as far as possible. Frequent measurements of calcium, phosphate and magnesium serum levels may be prudent in this patient population. The NCCN guidelines recommend denosumab or zoledronic acid in patients with prostate cancer who are positive for bone metastasis [60]. Denosumab, zoledronic acid and alendronate are also recommended for patients undergoing treatment with an androgen deprivation therapy for prostate cancer. In addition, the NCCN guidelines recognized that both denosumab and zoledronic acid have been shown to prevent disease-related skeletal complications, such as fracture, spinal cord compression, or the need for surgery or radiotherapy to bone in men with castration-recurrent prostate cancer. However, denosumab was shown to be superior to zoledronic acid in the prevention of SREs. The guidelines recommend the monitoring of patients for the detection of hypophosphatemia and hypocalcemia. In this patient population, denosumab may be administered to men with impaired renal function, including patients undergoing hemodialysis. However, these patients present a higher risk of severe hypocalcemia and hypophosphatemia; hence, frequent measurements of calcium and phosphate levels are required. In these patients, hypocalcemia should be corrected before starting denosumab, and serum calcium monitoring is required in patients treated with denosumab and recommended in patients treated with zoledronic acid. The NCCN guidelines [61] recommend the administration of bisphosphonates or denosumab for the treatment of bone metastases in NSCLC patients. According to the NCCN guidelines [59-61], frequent monitoring for the detection of hypocalcemia is recommended in patients with prostate cancer, breast cancer or NSCLC. Supplemental calcium and vitamin D treatment is also recommended in order to prevent hypocalcemia in these three populations receiving either denosumab or zoledronic acid.

In the recently published guidelines of the Spanish Society of Medical Oncology (SEOM) [62], the superiority of denosumab in comparison with zoledronic acid in preventing or delaying SREs in breast and prostate cancer was described. Moreover, SEOM guidelines also describe the noninferiority of denosumab in comparison with zoledronic acid in the treatment of bone metastases in other solid tumors and myeloma. SEOM guidelines highlight the convenient subcutaneous administration of denosumab and the fact that no dose adjustment is required in cases of renal impairment. These guidelines also state the fact that denosumab significantly increased the median metastasis-free survival in patients with high risk non-metastatic prostate cancer, according to results of a Phase III study of denosumab in comparison with placebo [63].

The updates of the American Society of Clinical Oncology (ASCO) guidelines are conducted according to an evidence-based pre-established protocol [64]. Denosumab was first added to the recommendations issued by ASCO guidelines in the update published in March 2011 for the treatment of patients with breast cancer and bone metastasis.

5. Conclusion

This review has highlighted the new clinical results about the superiority of denosumab over bisphosphonates in preventing SREs in cancer patients with bone metastases. The relevant findings relative to this comparison could be explained by

the known mechanisms of action of denosumab, which are different from those observed for bisphosphonates. In fact, these effects are related to RANKL inhibition. However, this mechanism of action could also clarify both the immunomodulatory and antitumor effects of denosumab. Denosumab has already gained the indication for SRE prevention in cancer patients with bone metastases. The adverse effects of denosumab are similar to those observed for bisphosphonates, except for the renal impairment and acute phase reactions, which arise less frequently in the patients treated with denosumab. Future researches should focus on antitumor activity of this drug to also improve OS as some initial findings suggested.

6. Expert opinion

Bone metastases represent a complication in a wide range of malignancies. In fact, the skeleton is generally the first, and sometimes the only, site of metastases in patients with an advanced tumor. Bone metastases cause considerable morbidity in patients. In addition, they are the most frequent cause of cancer-related pain. Owing to the improvement of therapies and survival rates in cancer patients, bone metastases are nowadays more frequently detected in patients. In this review, two types of agents administered for the prevention and treatment of cancer-related effects on bone have been reviewed. Bisphosphonates, particularly zoledronic acid, are reported as the best-known antiresorptive drugs. Denosumab, a monoclonal antibody which exerts its activity through the suppression of osteoclasts formation, provides a new approach for the prevention of cancer-related effects. Denosumab has been demonstrated to be superior to zoledronic acid in delaying and preventing SREs in a wide range of cancer types with bone metastases. In addition, in lung cancer, denosumab has demonstrated an improvement in survival compared with zoledronic acid.

With regard to the safety profile of both drugs, ONJ was an infrequent AE in patients treated with any of the agents. In patients treated with denosumab or with zoledronic acid, no significant differences in ONJ rates were found. However, hypocalcemia was more frequent in patients receiving denosumab. Thus, calcemia levels should be monitored in patients treated with denosumab to avoid severe symptomatic hypocalcemia that may include fatal cases [65]. On the other hand, renal monitoring was more frequently required in patients treated with zoledronic acid, with subsequent dose adjustment in some patients.

Last, in the recent update of ASCO guidelines, denosumab has been included for the treatment of patients with breast cancer and bone metastasis. The NCCN guidelines recognized that both denosumab and zoledronic acid have been shown to prevent disease-related skeletal complications, such as fracture, spinal cord compression, or the need for surgery or radiotherapy to bone in men with castration-recurrent prostate cancer, and also that denosumab was shown to be superior in the prevention of SREs in comparison with zoledronic acid in this patient population.

The SEOM guidelines also recognized the superiority of denosumab in comparison with zoledronic acid in patients with breast and prostate cancer with metastases to the bone. In addition, SEOM guidelines highlight the convenient subcutaneous administration of denosumab and the non-requirement for dose adjustment in patients with renal impairment. They also highlight the higher metastasis-free survival detected in patients with non-metastatic prostate cancer, according to results of a Phase III trial comparing denosumab versus placebo. Hence, denosumab represents a potential new treatment for the management of bone metastases across a broad range of solid tumor types.

The findings about new target drugs in metastatic prostate cancer allow us to contemplate that antitumor activity is strictly linked with the control of bone resorption and related symptoms. As previously found for zoledronic acid, denosumab also seems to have direct antitumor effects. This consideration is deduced by both preclinical findings and clinical outcome changes (i.e., OS) by denosumab. We propose that these effects could be a consequence of RANK and RANKL expression in tumor cells. The expression of these molecules in cancer cells suggests the hypothesis that the RANK–RANKL pathway has further functions beyond the regulation of bone resorption. Specific studies are needed to support this hypothesis. Denosumab should be tested in cancer cell lines, experimental models with tumor-bearing mice and translational studies evaluating the activity on metastases different from bone-related ones, and functional imaging could help to clarify these results.

Denosumab is actually a promising drug, which offers better opportunities in reducing the risk of SREs than bisphosphonates with less adverse effects. However, we could suppose that in the future years several studies will clarify the antitumor effects and could help in identifying the better combination of denosumab with other drugs.

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