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REVIEW

Comparative Review of Denosumab Versus Zoledronic Acid for the Reduction or Delay of Serious Complications Associated with Bone Metastases of Breast Cancer

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Abstract: Bone metastases can lead to serious problems such as fracture, spinal cord compression and severe bone pain and may require treatment with surgery or radiation therapy. The purpose of this paper is to discuss the comparative effects of denosumab (a novel, fully human, monoclonal antibody that inhibits the receptor activator of nuclear-factor-κB [RANK] ligand) and zoledronic acid (bisphosphonate) on the reduction or delay of serious complications associated with bone metastases in breast cancer patients. Medical literature on strictly conducted, randomized controlled trials was reviewed to understand the effects of denosumab and zoledronic acid on bone complications such as fracture, radiation to the bone, surgery to the bone, and spinal cord compression in breast cancer patients. The results of a phase 3 study showed that patients treated with denosumab remained free of bone complications longer than patients treated with zoledronic acid. The overall survival and time to cancer progression were similar among patients treated with zoledronic acid and patients treated with denosumab. Osteonecrosis of the jaw occurred with a similar frequency among patients treated with zoledronic acid and patients treated with denosumab. Based on the review of the literature, denosumab was more effective than zoledronic acid for delaying or preventing serious bone complications in breast cancer patients with bone metastases.

Keywords: breast cancer, bone metastasis, denosumab, RANKL, zoledronic acid

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Introduction

The skeleton is the most common site of tumor metastasis. Tumors of the breast and prostate are particularly likely to metastasize to the bone, with up to 70% of patients dying of advanced metastatic disease showing evidence of skeletal involvement.[1] Skeletal complications from bone metastases present a major challenge for disease management. Such complications, referred to as "skeletal-related events (SREs)", include fracture, radiation to the bone, surgery to the bone, and spinal cord compression.[2–4]

Metastatic bone disease is associated with a disruption of the normal coupling between bone formation and resorption, typically resulting in net osteolysis leading to the loss of structural integrity and subsequent skeletal events.[5] Bone-targeted drug therapy has been aimed at the disruption of this osteoclast-mediated bone resorption. Currently, intravenous bisphosphonates such as zoledronic acid and pamidronate are commonly used for the treatment of bone metastases in patients with breast cancer or multiple myeloma.[6–9] Zoledronic acid may be more effective than pamidronate for reducing the risk of skeletal complications in patients with bone metastases from breast cancer or osteolytic lesions of multiple myeloma.[7–9] However, not all patients respond to treatment, and toxicities can preclude the use of bisphosphonates in certain patient populations.[10–12] Therefore, the development of novel therapies that reduce bone damage is important for improving disease management.

Denosumab is a novel, fully human, monoclonal antibody. It inhibits the receptor activator of nuclear-factor-κB (RANK) ligand, resulting in the inhibition of osteoclast-mediated bone resorption. This drug is used for the treatment of postmenopausal women with osteoporosis at high risk of fractures, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy, using a 60 mg subcutaneous injection every 6 months. It is also under investigation for the treatment of bone metastases in patients with breast cancer, prostate cancer, other solid tumors or multiple myeloma using a 120 mg subcutaneous injection every 4 weeks.[13–17]

Although both potent anti-resorptive drugs play a pivotal role in the treatment of bone destruction induced by metastatic bone tumors and may be effective for preventing SREs, whether the occurrence of such serious bone complications differs between patients treated with denosumab and those treated with zoledronic acid remained unclear. The purpose of this paper is to discuss the role of denosumab in the treatment of breast cancer bone metastases and the comparative effect of denosumab and zoledronic acid on reducing or delaying serious complications of bone metastases among breast cancer patients with bone metastases by reviewing the relevant medical literature.

Randomized Controlled Trials (RCTs) of Zoledronic Acid in Breast Cancer Patients with Bone Metastases

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption, which is increased when cancer cells invade the bone. Thus, bisphosphonates may be effective for the treatment of skeletal complications in patients with bone metastases. Currently, intravenous bisphosphonates, such as zoledronic acid and pamidronate, are part of the standard treatment for managing complications arising from bone metastases.[6–9]

Zoledronic acid is more commonly used to reduce the risk of complications from bone metastases of breast cancer. A multicenter, randomized, double-blinded, placebo-controlled study was performed in Japan to investigate the one-year efficacy and safety of zoledronic acid for the treatment of bone metastases from breast cancer.[6] Zoledronic acid reduced the rate of SREs (fracture, spinal cord compression, and radiation or surgery to the bone) by 39%, the percentage of patients with at least one SRE by 20%, the delayed time-to-first SRE, and the risk of SREs by 41%. Zoledronic acid was well tolerated with a safety profile similar to that of the placebo group. Thus, the efficacy and safety of zoledronic acid were confirmed in women with bone metastases from breast cancer.

A subgroup analysis of an international, randomized, double-blinded study was performed to compare the one-year efficacy of zoledronic acid and pamidronate in breast cancer patients with at least one osteolytic lesion.[9] The proportion with an SRE (pathologic fracture, spinal cord compression, radiotherapy, or surgery to the bone) did not differ significantly between the two groups (48% vs. 58%), but the time until the

first SRE was significantly longer in the zoledronic acid group than in the pamidronate group (median, 310 days vs. 174 days). Thus, zoledronic acid was more effective than pamidronate for reducing skeletal complications in breast cancer patients with at least 1 osteolytic lesion. It was confirmed that zoledronic acid (4 mg) via a 15-minute intravenous infusion was more effective than pamidronate (90 mg) via a 2-hour intravenous infusion for reducing the risk of skeletal complications in patients with bone metastases from breast cancer.

Actions of Denosumab on Bone Resorption

RANK/RANKL/OPG system

The RANK/RANKL/OPG system plays an important role in regulating osteoclastogenesis and bone metabolism.[18,19] RANK ligand (RANKL) belongs to a member of the tumor necrosis factor superfamily and is expressed in osteoblasts and bone marrow stromal cells.[18,19] RANKL binds to and activates its receptor RANK expressed on the surface of precursor cells and mediates a key roles in the pathway required for the formation, function, and survival of the cells that resorb bone (osteoclasts).[18,19] Osteoprotegerin (OPG) is an endogenous decoy receptor, binds to RANKL, and inhibits RANK signaling.[18,19]

Actions of denosumab on bone resorption

Denosumab (known as AMG 162) is a fully human monoclonal antibody that binds to RANKL with high affinity and specificity and inhibits RANKL in a manner similar to that of OPG.[18,19] The fully human monoclonal antibody is derived from transgenic carrying human antibody genes. Denosumab blocks osteoclastogenesis and bone resorption and works through a different pathway from that of bisphosphonates. Denosumab neutralizes RANKL, thereby inhibiting the interaction of RANKL and its receptor RANK.[18,19] Inhibition of the RANK-RANKL interaction prevents receptor activation and the downstream signaling that is essential for the formation, function, and survival of mature osteoclasts, which are responsible for bone resorption.[18,19] On the other hand, bisphosphonates bind avidly to hydroxyapatite bone mineral surfaces and are selectively internalized by osteoclasts, leading to loss of the ruffled border and disturbance of the cytoskeleton, which in turn causes loss of actin rings, and inhibition of bone resorption.[20] Within the osteoclast, nitrogen-bisphosphonates inhibit the mevalonate pathway, the main target being farnesyl pyrophosphate synthase (FPPS).[20] FPPS inhibition causes loss of farnesyl, and geranylgeranyl, pyrophosphate, required for prenylation (ie, post-translational lipid modification), of signaling GTPases, such as Ras, Rho and Rac.[20] This leads to defective intracellular vesicle transport, and loss of prenylated proteins, ultimately leading to induction of apoptosis, via activation of the caspase cascade, and interference of processes.[20]

Role of Denosumab in the Treatment of Breast Cancer Bone Metastases

Mechanisms of breast cancer bone metastases

Bone is a common site for metastasis in breast cancer, and approximately 75% of all women with advanced breast cancer develop bone metastases.[21,22] Based on the radiographic appearance of bone metastases, breast cancer causes lytic, mixed, or osteosclerotic lesions. Usually, osteolytic lesions are predominant.[23,24] The metastasis of tumors to bone is encouraged by the bone microenvironment. Bone resorption by osteoclasts leads to production of a variety of growth factors, such as transforming growth factor-β (TGF-β), fibroblast growth factors (FGFs), platelet-derived growth factors (PDGFs), bone morphogenetic proteins (BMPs), and insulin-like growth factor 1 (IGF-1).[19] Elevated TGF-β leads to the production of parathyroid hormone-related peptide (PTHrP).[19] These factors activate osteoclasts, thus establishing a continuously destructive cycle referred to as a "vicious cycle" through the upregulation of RANKL and accelerated bone resorption.[19] The vicious cycle appears to be important for the establishment and progression of the tumor within the skeleton.

Role of denosumab in the treatment of breast cancer bone metastases

RANK/RANKL pathway is essential for normal bone homeostasis. However, this process occurs in excess when tumor cells are present in bone.[19] The "seed and soil relationship" of bone metastases of breast cancer is based on the hypothesis that a reciprocal interaction

between tumor cells and the bone microenvironment is necessary for the colonization and expansion of tumor cells in bone and that bone resorption, which is governed by the RANK/RANKL/OPG triad, plays a critical role in this process.[19] RANKL is a critical mediator of osteoclast differentiation, function, and survival and therefore is a key mediator in the vicious cycle of bone destruction in metastatic cancer.[19] Thus, RANKL is an appropriate target for reducing the osteolytic bone damage caused by breast cancer bone metastases. Elevated RANKL expression in patients with cancer has been used as a marker of disease severity and survival.[19] The elucidation of the role of the RANKL system in breast cancer bone metastases was a step in the development of a targeted therapy to prevent such lesions. Because RANKL inhibitors selectively target osteoclast differentiation, activation, and survival, denosumab provides a mechanism-based approach for inhibiting bone destruction in breast cancer patients.

RCTs of Denosumab in Breast Cancer Patients with Bone Metastases

Phase 1 study[13]

A randomized, double-blind, double-dummy, active-controlled, multicenter phase 1 study was performed to determine the efficacy and safety of denosumab in patients with breast cancer (n = 29) or multiple myeloma (n = 25) with radiologically confirmed bone lesions. Patients received a single dose of either denosumab (0.1, 0.3, 1.0, or 3.0 mg/kg, subcutaneously) or pamidronate (90 mg, intravenously). The bone antiresorptive effect was assessed by monitoring changes in the urinary and serum N-telopeptide (NTx) levels, and the pharmacokinetics of denosumab were also assessed. Following a single subcutaneous dose of denosumab, the levels of urinary and serum NTx decreased within 1 day, and this decrease lasted for 84 days at the higher denosumab doses (urinary NTx: Fig. 1). Pamidronate decreased bone resorption, but the effect diminished progressively throughout the follow-up period (urinary NTx: Fig. 1). Denosumab was well tolerated. The mean half-lives of denosumab were 33.3 and 46.3 days for the two highest dosages (Fig. 2). These results indicated that a single subcutaneous dose of denosumab given to patients with multiple myeloma or bone metastases from breast cancer was well tolerated and reduced bone resorption for at least 84 days. The decrease in bone resorption was similar in magnitude but more sustained with denosumab than with pamidronate.

Phase 2 study

Results after 13 weeks[14]

A randomized, active-controlled, international, multicenter, multidose, parallel group phase 2 study was performed to evaluate the efficacy and safety of five dosing regimens of denosumab in patients with breast cancer-related bone metastases not previously treated with intravenous bisphosphonates. The primary endpoint was the median percentage change in urinary NTx from baseline to week 13. The secondary endpoints included the proportion of patients achieving a more than 65% reduction in urinary NTx from baseline, the median time to achieve this reduction, and the percentage of patients experiencing an SRE during the study period (fracture, surgery or radiation to bone, or spinal compression) as well as the safety. Intravenous bisphosphonate naïve women (n = 255) with breast cancer-related bone metastases were randomly assigned to one of six groups (five denosumab groups and one open-label intravenous bisphosphonate group). Denosumab was administered subcutaneously every 4 weeks (30, 120, or 180 mg) or every 12 weeks (60 or 180 mg). At study week 13, the median percent reduction in urinary NTx was 71% for the pooled denosumab groups and 79% for the bisphosphonate group (Fig. 3). Overall, 74% of the denosumab-treated patients achieved a more than 65% reduction in urinary NTx, compared with a reduction of 63% among bisphosphonate-treated patients. SREs were experienced during the study period by 9% of the denosumab-treated patients and 16% of the bisphosphonate-treated patients. No serious or fatal adverse events related to denosumab occurred. These results suggested that subcutaneous denosumab was similar to intravenous bisphosphonates in suppressing bone turnover and reducing the SRE risk, with a safety profile consistent with that of an advanced cancer population receiving systemic therapy.

In this study, the administration of denosumab every 4 weeks resulted in a numerically greater extent of urinary NTx suppression than administration every 12 weeks, with the group receiving a dose of 120 mg every 4 weeks showing the greatest overall median suppression in urinary NTx at the end of study

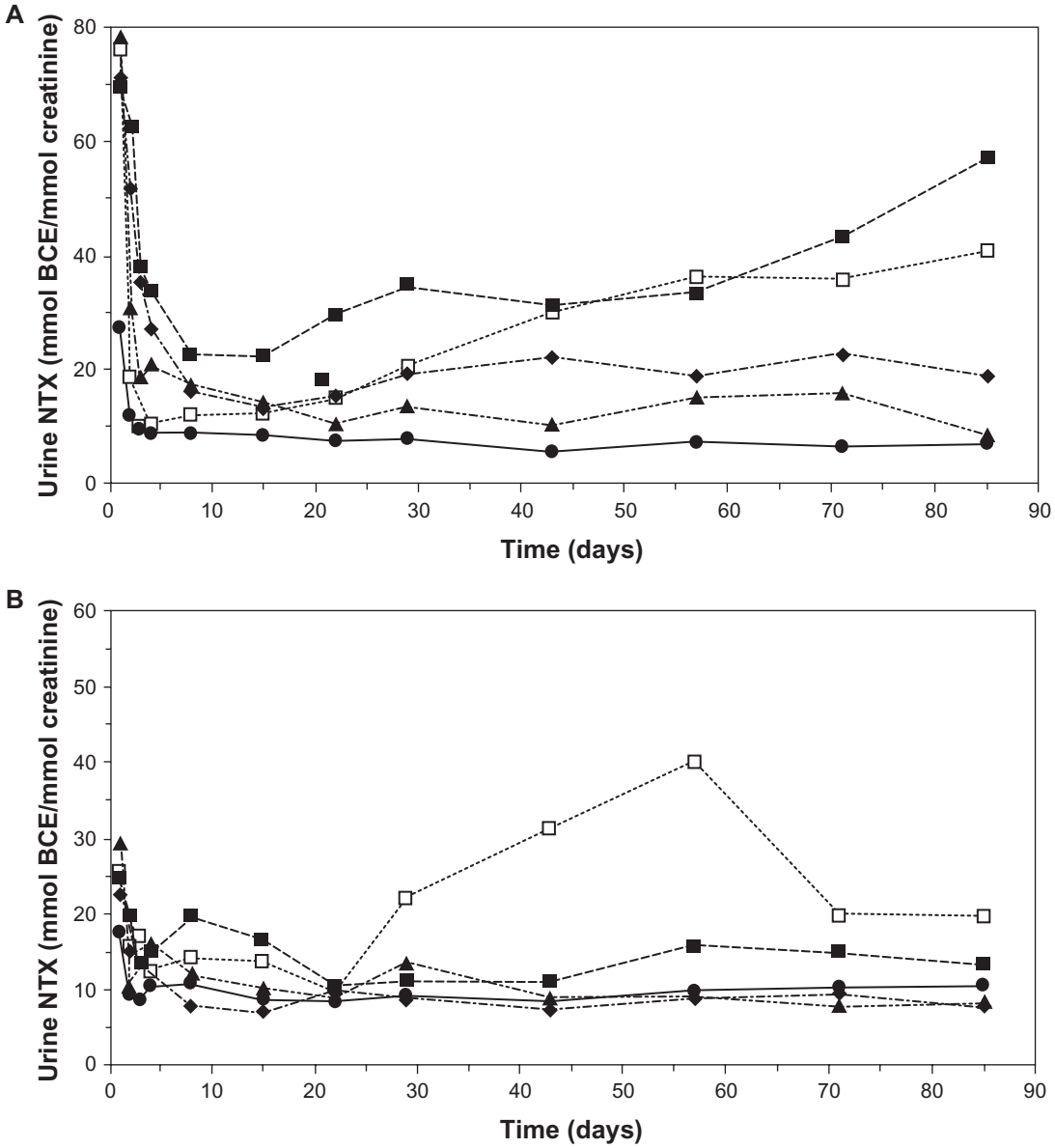

Figure 1. The pharmacodynamic effects of denosumab treatment on bone resorption; absolute median values of second-morning-void urinary NTx/creatinine in patients with breast cancer (**A**) and multiple myeloma (**B**) [Fig. 2 of reference #13].
Notes: □: pamidronate 90 mg i.v.; ■: denosumab 0.1 mg/kg s.c.; ♦: denosumab 0.3 mg/kg s.c.; ▲: denosumab 1.0 mg/kg s.c.; ●: denosumab 3.0 mg/kg s.c.
Abbreviations: NTx, N-telopeptide; BCE, bone collagen equivalent; i.v., intravenous; s.c., subcutaneous.

week 13 (Fig. 3). Based on this result, a denosumab dose of 120 mg every 4 weeks was selected for use in phase 3 clinical trials in cancer patients with bone metastases.

Results after 25 weeks[15]

The final (up to 25 weeks) efficacy results of the phase 2 study were also reported. At weeks 13 and 25, the median percent changes in urinary NTx among the patients with measurable urinary NTx levels were −73% and −75% for the pooled denosumab groups and −79% and −71% for the bisphosphonate group (Fig. 4). Among the patients with a ≥1 post-baseline urinary NTx measurement at week 25, 52% of the denosumab-treated patients and 46% of the bisphosphonate-treated patients achieved a >65% urinary NTx reduction (Fig. 4). SREs during the study period occurred in 12% of the denosumab-treated patients and 16% of the bisphosphonate-treated patients (Fig. 5). The overall rates of adverse events were 95% in the denosumab and bisphosphonate groups. No denosumab-related serious or fatal

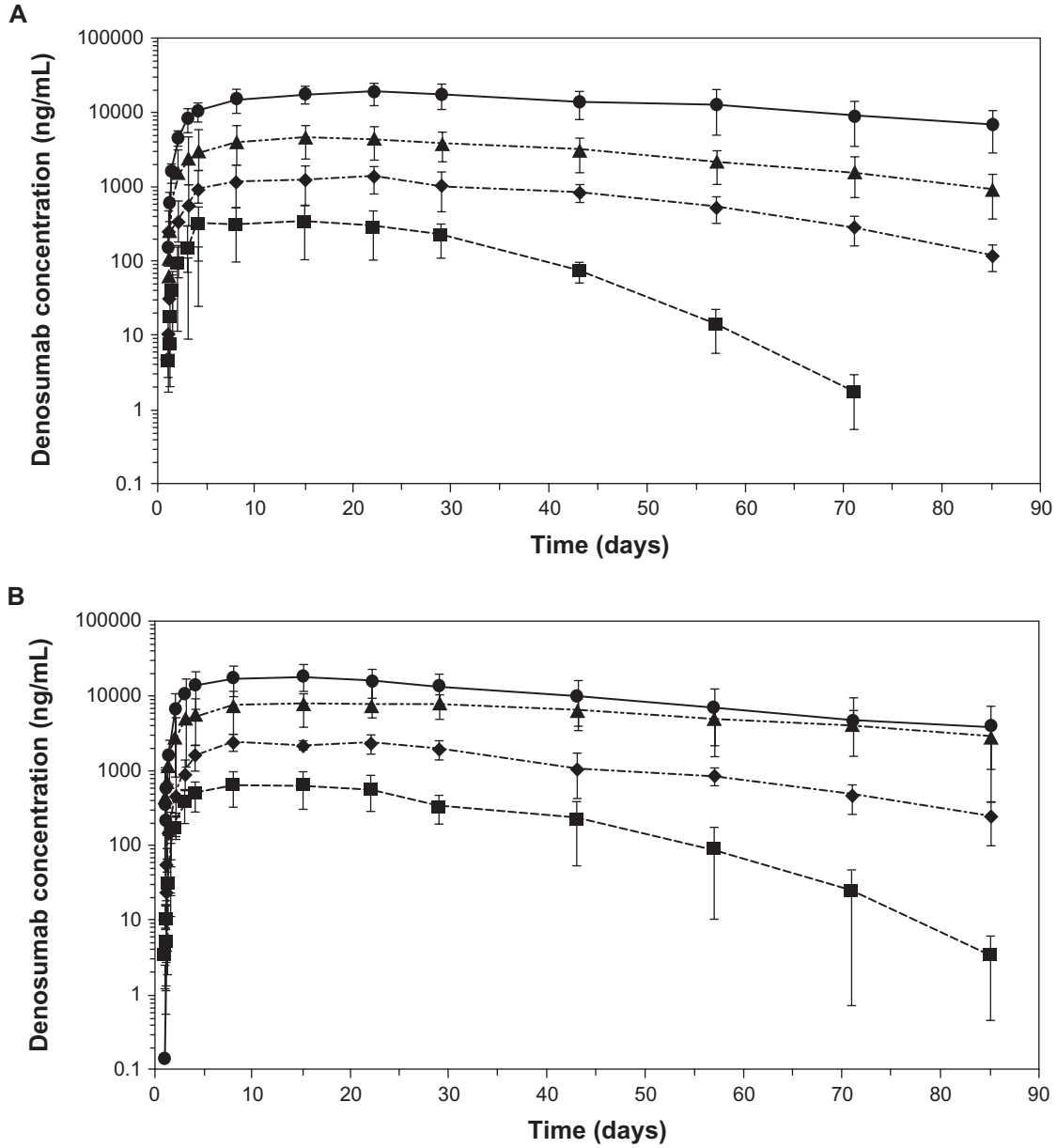

Figure 2. Pharmacokinetic profile of denosumab after a single s.c. dose: mean serum concentration in patients with breast cancer (**A**) and multiple myeloma (**B**) [Fig. 4 of reference #13].
Notes: Data are presented as mean ± standard deviation. ■: denosumab 0.1 mg/kg s.c.; ♦: denosumab 0.3 mg/kg s.c.; ▲: denosumab 1.0 mg/kg s.c.; ●: denosumab 3.0 mg/kg s.c.
Abbreviation: s.c., subcutaneous.

adverse events occurred. These results suggested that denosumab suppressed bone turnover and reduced the risk of SRE similarly to intravenous bisphosphonate, with a safety profile consistent with an advanced cancer population receiving systemic therapy. Although these data are promising, larger studies with a greater statistical power are needed to more firmly establish the effect of denosumab on the risk of SRE.

Phase 3 study[16]

A large multicentre, randomized, double-blind, active-controlled phase 3 study was performed to evaluate the efficacy and safety of denosumab vs. zoledronic acid in patients with advanced breast cancer and confirmed bone metastases without prior or current intravenous bisphosphonate use. Currently, only an abstract is available regarding this phase 3 study. The primary endpoint was the time until the

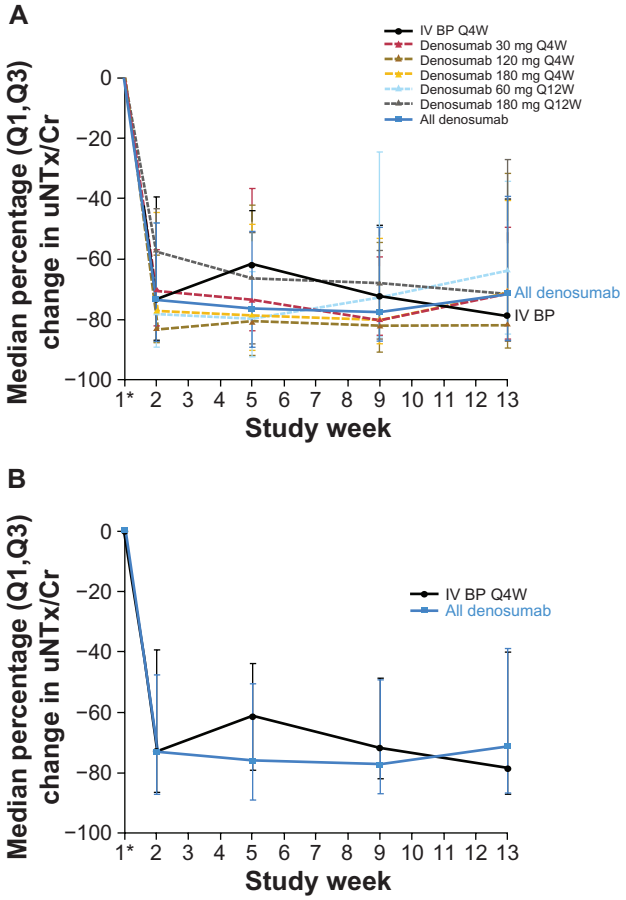

Figure 3. Median (Q1, Q3) percentage reduction in urinary NTx/Cr from baseline in patients with breast cancer-related bone metastases [Fig. 1 of reference #14]. Denosumab dose groups vs. IV BP (**A**) and all denosumab vs. IV BP (**B**).
Note: *Study week 1 = baseline.
Abbreviations: uNTx, urinary N-telopeptide; Cr, creatinine; IV BP, intravenous bisphosphonate; Q4W, every 4 weeks; Q12W, every 12 weeks.

first SRE during the study period as a non-inferiority measure. The secondary endpoints included the same as a superiority measure plus the time to first and subsequent SRE during the study period. SREs were regarded as fracture, radiation to the bone, surgery to the bone, and spinal cord compression. Patients were randomized to an intravenous zoledronic acid (4 mg) with subcutaneous placebo group (n = 1,020) or a subcutaneous denosumab (120 mg) with intravenous placebo group (n = 1,026); both regimens were administered every 4 weeks. Denosumab significantly delayed the time until the first SRE during the study period, compared with zoledronic acid (Hazard ratio [HR]: 0.82, 95% confidence interval [CI]: 0.71–0.95, $P = 0.01$). The median time until the first SRE for zoledronic acid was 806 days, while the median time until the first SRE was not reached in the denosumab group. Thus, the time-to-first SRE during the study period revealed a significant benefit for denosumab treatment over zoledronic acid with regard to both non-inferiority and superiority. Denosumab was also superior to zoledronic acid for a multiple event analysis of the time to first and subsequent SREs during the study period. In contrast, no differences across the treatments were observed for overall survival, and overall disease progression. Adverse events across the treatment groups were similar. Osteonecrosis of the jaw (ONJ) occurred in 2% of the patients receiving denosumab and 1.4% of the patients in the zoledronic acid group ($P = 0.39$). These results suggested that denosumab was well tolerated and superior to zoledronic acid for delaying the time until the first SRE and successive events.

Discussion: Comparison of Denosumab and Zoledronic Acid on the Treatment of Complications in Breast Cancer Patients with Bone Metastasis

Zoledronic acid may be effective for reducing morbidity and subsequent mortality in breast cancer patients with bone metastases. However, not all patients respond to treatment, and renal toxicity and ONJ can preclude the use of intravenous bisphosphonates, such as zoledronic acid and pamidronate, in certain patient populations.[10–12] Therefore, developing novel therapies that reduce bone damage is important for improving disease management. Despite the availability of potent bisphosphonates, such as zoledronic acid, an unmet medical need exists for a more convenient, safe, and effective therapy.

Because RANKL is a key mediator in the vicious cycle of bone destruction in metastatic cancer, denosumab may provide a mechanism-based approach for inhibiting bone destruction in breast cancer patients. A phase 2 study (25 weeks) showed that the median percent change in urinary NTx among patients was −75%, and that 52% of the denosumab-treated patients achieved a >65% urinary NTx reduction.[15] A reduction of more than 65% was chosen because this was the average percentage decrease reported in medical literature for patients with bone metastases

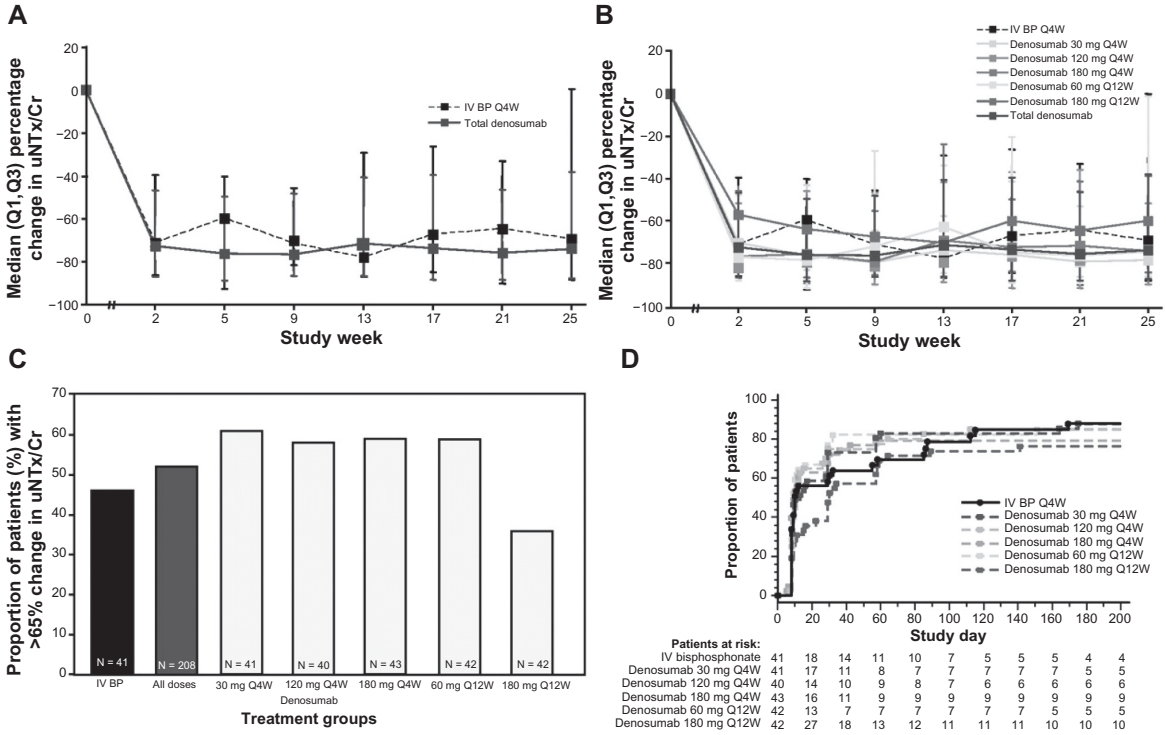

Figure 4. Effects of denosumab and IV BP on urinary NTx/Cr in patients with breast cancer-related bone metastases [Fig. 1 of reference #15]. All doses of denosumab resulted in suppression of uNTx/Cr; suppression was seen at the first study visit after administration of the initial dose and continued through week 25 (**A**). At week 25, the median percentage change from baseline in uNTx/Cr was similar in both treatment groups (**B**). At week 25, 52% of denosumab-treated patients had a uNTx/Cr reduction of >65%, as did 46% of IV BP-treated patients (**C**). A Kaplan-Meier analysis shows that the time to a uNTx/Cr reduction of >65% was similar in all treatment groups, except for the denosumab 180 mg Q12 dose group (**D**).
Abbreviations: uNTx, urinary N-telopeptide; Cr, creatinine; IV BP, intravenous bisphosphonate; Q4W, every 4 weeks; Q12W, every 12 weeks.

treated with intravenous bisphosphonates.[25–28] SREs during the study period occurred in only 12% of the denosumab-treated patients. Breast cancer patients with bone metastases are characterized by elevated levels of bone turnover markers, such as urinary NTx; patients with elevated levels of urinary NTx are at an increased risk for skeletal complications, disease progression, and death.[5,14,29,30] The inhibition of osteoclast function, as measured by decreases in bone resorption, may result in fewer skeletal complications

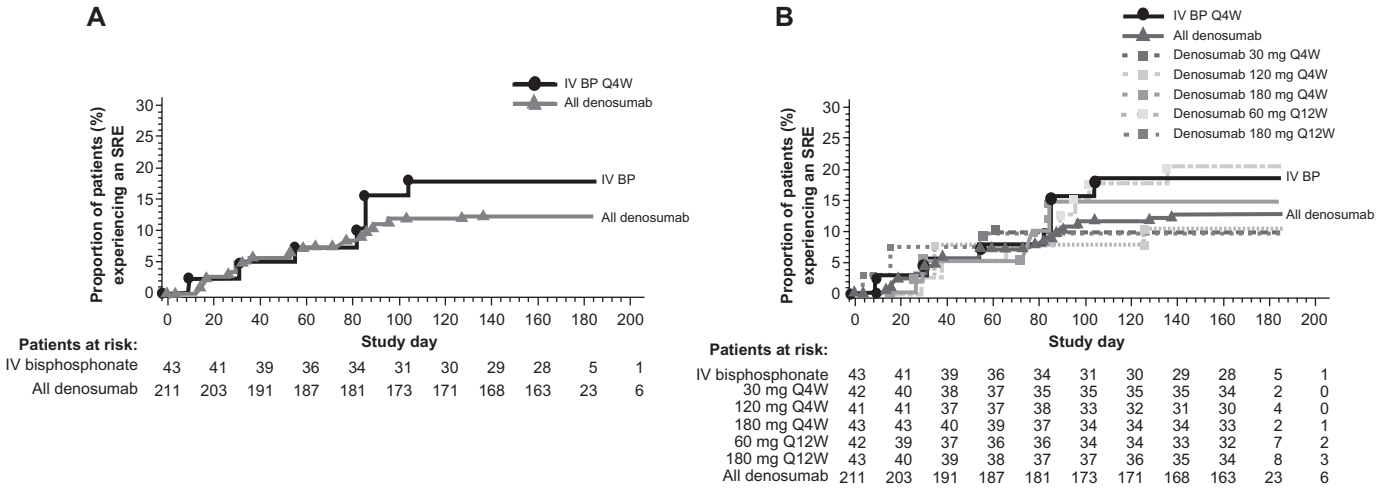

Figure 5. Effects of denosumab and IV BP on the occurrence of SREs in patients with breast cancer-related bone metastases [Fig. 3 of reference #15].
Note: By the end of the study, 26 patients (12%) in the denosumab groups and 7 patients (16%) in the IV BP group had experienced at least 1 SRE.
Abbreviations: SRE, skeletal-related event; IV BP, intravenous bisphosphonate; Q4W, every 4 weeks; Q12W, every 12 weeks.

and a more favorable prognosis. Recent data show a link between the normalization of the bone resorption rate, as evaluated by NTx determination, and the beneficial effects of zoledronic acid on complications associated with tumor bone disease.[5,29] The results of the phase 2 study suggested that denosumab suppressed bone turnover and reduced the risk of SREs.

A phase 3 study showed that denosumab-treated patients remained free of bone complications (fracture, radiation to the bone, surgery to the bone, and spinal cord compression) longer than zoledronic acid-treated patients.[16] These results indicated that denosumab was more effective than zoledronic acid at delaying or preventing skeletal complications in breast cancer patients with bone metastases. This greater efficacy could be partly due to the prolonged circulatory residence time of denosumab. Denosumab is administered as a subcutaneous bolus injection, eliminating the need for intravenous infusion.

In patients with bone metastases from castration-resistant prostate cancer, a randomized phase 3 trial of denosumab vs. zoledronic acid also showed that denosumab significantly delayed the time-to-first SRE compared with zoledronic acid (median, 20.7 months vs. 17.1 months), with similar overall survival and time to cancer progression.[31] Overall adverse event rates and serious adverse events were similar between treatment groups. Hypocalcemia was reported in 13% of denosumab patients and 6% zoledronic acid patients. ONJ was reported in 2.3% of denosumab patients and 1.3% of zoledronic acid patients ($P = 0.09$). Denosumab demonstrated superiority over zoledronic acid in delaying or preventing SREs in patients with bone metastases from castration-resistant prostate cancer.

Renal toxicity and ONJ are potential complications of zoledronic acid.[10–12] A phase 3 study in patients with advanced breast cancer showed that denosumab was less toxic with regard to renal toxicities.[16] The inhibition of RANKL does not result in the release of cytokines that might stimulate an acute phase reaction. The tolerability of denosumab seems to be another potential advantage. Other major adverse events were similar between denosumab and zoledronic acid. In particular, ONJ occurred among patients treated with denosumab for breast cancer bone metastasis with a similar incidence to that among those treated with zoledronate.[16] ONJ appears to be a class effect of osteoclast-inhibiting drugs.

In the phase 3 study, advance breast cancer patients were recruited even if they had experienced a previous SRE, or were currently undergoing chemotherapy.[16] Determining whether denosumab can prevent the occurrence of bone metastases in early-stage breast cancer patients is of great importance. Future directions of denosumab therapy may include the prevention of bone metastases as a primary endpoint in early-stage breast cancer patients.

Conclusions

This paper discussed the role of denosumab in the treatment of bone metastases of breast cancer and compared the effects of denosumab and zoledronic acid on the reduction or delay of serious complications of bone metastases among breast cancer patients with bone metastases by reviewing the available medical literature. Because RANKL is a key mediator in the vicious cycle of bone destruction in metastatic cancer, denosumab provides a mechanism-based approach for inhibiting bone destruction in breast cancer patients. The results of a phase 3 study showed that denosumab was more effective than zoledronic acid at delaying or preventing bone complications in breast cancer patients with bone metastases. Thus, denosumab showed promising results for the management of breast cancer patients with bone metastases.

Disclosure

The study was not supported by any grant. This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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