Bone-Related Complications and Quality of Life in Advanced Breast Cancer: Results from a Randomized Phase III Trial of Denosumab versus Zoledronic Acid

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Abstract

Purpose: Denosumab was shown to be superior to zoledronic acid in preventing skeletal related events (SRE) in patients with breast cancer and bone metastases in a randomized, double-blind phase III study. We evaluated further results from this study related to skeletal complications and health-related quality of life (HRQoL).

Experimental Design: Patients were randomized 1:1 to receive subcutaneous denosumab 120 mg (n = 1,026) and intravenous placebo, or intravenous zoledronic acid 4 mg (n = 1,020) and subcutaneous placebo every 4 weeks. Analyses reported here include the proportion of patients with one or multiple on-study SREs, time to first radiation to bone, time to first SRE or hypercalcemia of malignancy, and change in HRQoL (functional assessment of cancer therapy–general).

Results: Fewer patients receiving denosumab than zoledronic acid had an on-study SRE (31% vs. 36%, P = 0.006). The incidence of first radiation to bone was 12% (n = 123) with denosumab versus 16% (n = 162) with zoledronic acid. Denosumab prolonged the time to first radiation to bone by 26% versus zoledronic acid (HR, 0.74; 95% confidence interval [CI], 0.59–0.94, P = 0.012) and prolonged the time to first SRE or hypercalcemia of malignancy by 18% (HR, 0.82; 95% CI, 0.70–0.95; P = 0.007). Ten percent more patients had a clinically meaningful improvement in HRQoL with denosumab relative to zoledronic acid, regardless of baseline pain levels.

Conclusions: Denosumab was superior to zoledronic acid in reducing bone-related complications of metastatic breast cancer and maintained HRQoL, providing an efficacious, well-tolerated treatment option for patients with bone metastases from breast cancer. Clin Cancer Res; 18(17); 4841–9. ©2012 AACR.

Introduction

Clinical manifestations of bone metastases include hypercalcemia of malignancy, a reversible but potentially life-threatening consequence of advanced disease (1), and the local irreversible skeletal related events (SRE) of pathologic fracture, spinal cord compression, and radiation to bone or surgery to bone (1). For patients with breast cancer and bone metastases, the occurrence of any SRE is associated with poorer physical, functional, and emotional status and poorer overall quality of life (2, 3). Along with pain, SREs can reduce patients’ functional independence, ability to care for themselves, and involvement in normal daily activities (2). SREs also increase patients’ risk of hospitalization and the duration of hospital stays (4). Prevention of SREs in patients with breast cancer has been shown to reduce pain and to improve the physical, emotional, functional, and social aspects of quality of life (3, 5, 6). Intravenous bisphosphonates, which reduce or delay the occurrence of SREs, have been part of the standard of care
for patients with breast cancer and bone metastases (7). Nonetheless, up to 47% of breast cancer patients with bone metastases experience SREs while receiving treatment with the commonly used bisphosphonate zoledronic acid (8–10). In addition, the use of zoledronic acid requires intravenous access (e.g., an intravenous port) and may cause renal toxicity and acute-phase reactions (11). More effective, safer, and more tolerable therapies are needed to prevent SREs and their detrimental effects on quality of life.

Metastatic tumor cells in bone release cytokines and growth factors that stimulate increased expression of RANK ligand (RANKL; ref. 12), which in turn promotes increased osteoclastic activity, resulting in significant bone destruction. Denosumab is a monoclonal antibody against RANKL, with a targeted mechanism of action distinct from that of bisphosphonates, which have been widely used to prevent skeletal complications in patients with advanced cancer. In this phase III clinical trial, denosumab 120 mg administered subcutaneously every 4 weeks showed significant benefit over the intravenous bisphosphonate zoledronic acid 4 mg every 4 weeks across multiple outcomes, including local irreversible skeletal complications (skeletal related events), the development of hypercalcemia of malignancy, and health-related quality of life.

Patients and Methods

This international, randomized, double-blind, double-dummy, parallel-group study compared denosumab (XGEVA, Amgen Inc.) with zoledronic acid (Zometa, Novartis Pharmaceuticals) for the prevention of SREs in patients with advanced breast cancer. The study design was identical to that of 2 other recently reported phase III studies of denosumab in advanced cancer (14, 15) and was approved by the Institutional Review Board or ethics committee for each research site. All patients were required to provide written informed consent. The study was registered at http://www.clinicaltrials.gov, identifier NCT00321464.

Eligible patients were 18 years of age or older, with histologically or cytologically confirmed breast adenocarcinoma, at least one bone metastasis, adequate organ function, and Eastern Cooperative Oncology Group (ECOG) performance status 2 or less.

Procedures

Patients were randomly assigned (1:1) to receive, every 4 weeks, denosumab 120 mg as a single subcutaneous injection and intravenous placebo or zoledronic acid 4 mg (adjusted for renal function per zoledronic acid prescribing information) as an intravenous infusion over at least 15 minutes and subcutaneous placebo. Daily supplementation with calcium (≥500 mg) and vitamin D (≥400 IU) was strongly recommended to all patients. Treatment assignments were made via an interactive voice response system using permuted blocks with a block size of 4. The randomization schedule was computer-generated, prepared before study initiation by an independent individual who had no access to study data. Patients, caregivers, investigators, and staff were blinded to treatment assignments until completion of the primary analysis. An independent external data monitoring committee met twice yearly to monitor patient safety and drug efficacy; committee members were not blinded to treatment assignments.

Endpoints

The primary and secondary endpoints of this study [time to first on-study SRE and time to first-and-subsequent on-study SREs (multiple event analysis)] and the safety and tolerability of denosumab in this population have been reported (13). Prespecified exploratory endpoints included in this article are the proportion of patients with one or multiple SREs on study, time to first radiotherapy to bone, and time to first SRE or hypercalcemia of malignancy. Hypercalcemia of malignancy was defined as a serum calcium value (albumin adjusted, if necessary) more than 2.9 mmol/L or more than 11.5 mg/dl or ionized calcium more than 1.5 mmol/L determined from central laboratory data. We also compared the incidence of SREs during denosumab treatment with that of the incidence for placebo, based on the results of placebo-controlled registration studies of zoledronic acid (16–18). Number-needed-to-treat (NNT) analyses were carried out ad hoc to describe the number of patient-years of treatment with denosumab, compared with zoledronic acid or placebo, needed to prevent one SRE.

We also report clinically meaningful change in health-related quality of life (HRQoL), defined as a 5-point change or more from baseline on the 27-item functional assessment of cancer therapy–general (FACT-G) questionnaire (19, 20). FACT-G evaluates the HRQoL domains of physical, functional, social/family, and emotional well being in patients with cancer. The FACT-G has a 5-point response scale in which patients indicate how much of a problem from 0 (not at all) to 4 (very much) each item has been in the previous 7 days. HRQoL is reported overall and for subgroups based on worst pain severity score at baseline as

Translational Relevance

Metastatic tumor cells in bone release cytokines and growth factors that stimulate increased expression of RANK ligand (RANKL), which promotes increased osteoclastic activity that may result in significant bone destruction and debilitating skeletal complications. Denosumab is a monoclonal antibody against RANKL, with a targeted mechanism of action distinct from that of bisphosphonates, which have been widely used to prevent skeletal complications in patients with advanced cancer. In this phase III clinical trial, denosumab 120 mg administered subcutaneously every 4 weeks showed significant benefit over the intravenous bisphosphonate zoledronic acid 4 mg every 4 weeks across multiple outcomes, including local irreversible skeletal complications (skeletal related events), the development of hypercalcemia of malignancy, and health-related quality of life.

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recorded on the brief pain inventory short form (BPI-SF; ref. 21), an instrument on which a patient selects a value on a visual rating scale from 0 to 10 to represent the level of pain. Changes from baseline in ECOG performance status are also reported, as are detailed data about adverse events (AE) potentially associated with acute-phase reactions that occurred within the first 3 days after treatment. We also report data with regard to renal toxicity identified from prespecified terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0, as well as dose adjustments and dose withholding because of renal impairment at baseline or renal deterioration on study.

**Statistical methods**

The statistical methods used for analyses of key study endpoints have been described previously (13). Efficacy analyses included all randomized patients. The safety analyses included all randomized patients who received at least one dose of investigational product. HRQoL data were analyzed for all randomized patients who completed the FACT-G questionnaire at baseline. For HRQoL analyses by worst pain severity score at baseline on the BPI-SF, data were analyzed for all randomized patients who completed the FACT-G and BPI-SF at baseline. Analyses were conducted for data through month 18, when 30% of patients had discontinued the study because of death, disease progression, or withdrawal of consent.

Continuous and categorical variables were summarized using descriptive statistics; time-to-event variables were analyzed using the Kaplan–Meier method. The HR and associated 2-sided 95% confidence intervals (CI) were determined using a Cox proportional hazards model. The χ² test was used to produce the P values for comparing proportions between treatment groups. The significance level for each exploratory efficacy endpoint was 0.05 (2-sided) without adjusting for multiplicity. The statistical comparison of denosumab with placebo for the time to first SRE on study was based on the assumption that the zoledronic acid effect compared with placebo in this study was similar to that observed in the corresponding zoledronic acid and pamidronate registrational studies (17, 18); that is, that there was constancy of treatment effect of bisphosphonates over the different studies, per the method reported previously (13). On the basis of event-driven nature of the study, the NNT for denosumab versus zoledronic acid was calculated as the inverse of the difference of the patient-year adjusted rates between 2 treatments in the time to first or first and subsequent on-study SRE (or, for patients without an SRE, time to the end of the study, or primary analysis data cutoff date, whichever occurred first). In the calculation of NNT, every event was counted, with no 21-day window applied (13), to ensure that every event would be reflected. The NNT for denosumab versus placebo for the prevention of first on-study SREs was calculated using data from the zoledronic acid and pamidronate registrational studies (17, 18).

**Results**

Patients (n = 1,026 denosumab, n = 1,020 zoledronic acid) were randomized over a 20-month period. Baseline demographics and disease characteristics were balanced (Table 1) (13). At least one dose of investigational product was administered to 1,020 patients in the denosumab group and 1,013 patients in the zoledronic acid group.

Denosumab was superior to zoledronic acid in prolonging the time to first on-study SRE and reducing the risk of first SREs, as previously reported (13). Fewer first SREs occurred on study in the denosumab group than in the zoledronic acid group (denosumab, 315 first SREs in 1,065 patient-years; zoledronic acid, 372 first SREs in 1,040 patient-years), resulting in an NNT for denosumab compared with zoledronic acid of 16 patient-years. Thus, treatment of 16 patients per year with denosumab rather than zoledronic acid is expected to prevent one additional first SRE. Denosumab was also superior to zoledronic acid in preventing first-and-subsequent on-study SREs (multiple event analysis, previously reported; ref. 13). Over the 1,353 patient-years observed in both treatment groups, 660 SREs occurred in the denosumab group and 853 SREs in the zoledronic acid group, yielding an NNT of 7 for denosumab to prevent one first or subsequent SRE compared with zoledronic acid. In a statistical analysis comparing the rates of SREs observed with denosumab to those with placebo based on the results of the registrational studies of zoledronic acid and pamidronate (16–18), denosumab reduced the risk of developing a first SRE by 48%. The NNT with denosumab compared with placebo was 4 patient-years, indicating that, on average, treatment of 4 patients with denosumab for one year is expected to prevent one additional first SRE compared with no treatment.

Fewer patients in the denosumab group than in the zoledronic acid group experienced an SRE on study (31% vs. 36%, P = 0.006; Fig. 1A). Among patients with at least one on-study SRE, the proportion of patients who had multiple SREs on study was also numerically lower with denosumab than with zoledronic acid: 33% versus 38%, P = 0.16 (Fig. 1B). In the subgroup of patients with a history of prior SRE at study entry (Table 1), fewer patients in the denosumab group than in the zoledronic acid group experienced one or more subsequent SREs while on study (36% vs. 44%, P = 0.021). Similarly, among patients who had no history of SREs at study entry, 28% of patients in the denosumab group and 32% in the zoledronic acid group experienced their first SRE while on study (P = 0.085).

The incidence of first radiation therapy to bone was 12% (n = 123) with denosumab versus 16% (n = 162) with zoledronic acid. Denosumab prolonged the time to radiation therapy to bone by 26% compared with zoledronic acid (HR, 0.74; 95% CI, 0.59–0.94, P = 0.012, Fig. 2A). Denosumab also reduced the risk of developing an SRE or hypercalcemia of malignancy by 18% (HR, 0.82; 95% CI, 0.70–0.95, P = 0.007). The median time to first on-study SRE or hypercalcemia was not reached for denosumab and was 25.2 months for zoledronic acid (Fig. 2B).
Approximately half as many events of hypercalcemia occurred with denosumab as with zoledronic acid (28 vs. 58 events, rate ratio 0.48; 95% CI, 0.24–0.95, \( P = 0.036 \)).

Among patients with first on-study SREs, fewer patients in the denosumab group had pathologic fractures (denosumab 21%, zoledronic acid 23%) or radiation to bone (denosumab 82 patients, 8%; zoledronic acid 119 patients, 12%). First SREs of surgery to bone and spinal cord compression were each reported in approximately 1% of patients in each treatment group.

The median FACT-G total score at baseline was 74 for both treatment groups, which is consistent with results observed in other patients with metastatic breast cancer (22). In the overall population, over monthly time points
during an 18-month period, an average of 10% more patients in the denosumab group compared with the zoledronic acid group had a clinically meaningful improvement in HRQoL (≥5-point increase in FACT-G total score) over the course of the study (34% vs. 31%; Fig. 3A). An average of 7% fewer patients in the denosumab group than in the zoledronic acid group had worsening of HRQoL on study. The positive effect of denosumab treatment on HRQoL was observed regardless of pain severity at baseline. Among patients with no or mild pain at baseline (BPI-SF score 0 to 4), the relative overall improvement in HRQoL was 14% greater with denosumab compared with zoledronic acid (Fig. 3B). Among patients who had moderate or severe pain at baseline (BPI-SF score 5 to 10), the relative overall improvement in HRQoL was 9% greater with denosumab than with zoledronic acid.

ECOG performance status was maintained during the study by 59% and 55% of patients in the denosumab and zoledronic acid groups, respectively.
zoledronic acid groups, respectively. Worsened ECOG performance status was reported for 36% of patients in the denosumab group and 41% of patients in the zoledronic acid group; improved ECOG status was reported in 5% and 4% of patients in the denosumab and zoledronic acid groups, respectively.

As required per zoledronic acid prescribing information, its initial doses were adjusted to levels less than 4 mg in 131 patients (13%) and 245 doses were withheld in 56 patients (6%) on study because of serum creatinine increases. No dose adjustment or dose withholding for renal dysfunction was required for denosumab. Despite these measures, the incidence of AEs associated with renal toxicity was lower in the denosumab group (50 patients; 4.9%) than in the zoledronic acid group (86 patients; 8.5%; \( P = 0.001 \)).

The incidence of renal AEs in denosumab-treated patients was as expected in patients with advanced cancer and was lower than the 6.7% rate of increased serum creatinine reported in the placebo group in the pivotal study of zoledronic acid in patients with solid tumors and bone metastases (23). No patients in the denosumab group and 3 patients (0.3%) in the zoledronic acid group withdrew from investigational product because of renal failure.

Acute-phase reactions associated with a flu-like syndrome within the first 3 days after treatment, including pyrexia, fatigue, bone pain, chills, arthralgia, and headache, were less frequent with denosumab than with zoledronic acid (overall \( P < 0.0001 \), Fig. 4). No acute-phase reaction AEs were attributed to denosumab. Serious AEs associated with acute-phase reactions were reported in no patients (0%) treated with denosumab and 10 patients (1%) treated with zoledronic acid during the first 3 days after initial treatment, including pyrexia (\( n = 7 \)), bone pain (\( n = 2 \)), asthenia, back pain, chest pain, chills, headache, and malaise (one patient each). Some patients experienced more than one event. Eight of the 10 patients in the zoledronic acid group with serious acute-phase reaction AEs were hospitalized or had their hospitalization prolonged as a result of these events. Three patients with serious acute-phase reaction AEs discontinued zoledronic acid treatment after the first dose.

Over the 34 months of treatment included in this analysis, the patient incidence of pyrexia in denosumab-treated patients (16.7%; ref. 13) was approximately half the incidence of pyrexia in the placebo groups in a 12-month study of zoledronic acid in patients with advanced breast cancer (32.7%; ref. 16) and in 3 studies of pamidronate versus placebo (32%–38%; ref. 24), suggesting that the acute-phase reaction events observed with denosumab represent the background rate expected in this population.

**Discussion**

In this study of more than 2,000 patients with advanced breast cancer, denosumab reduced the risk of skeletal complications across many different efficacy measures, irrespective of SRE history. Fewer patients treated with denosumab than with zoledronic acid had first SREs, multiple SREs,
pathologic fractures, radiation therapy to bone, or hypercalcemia. On average, treatment of 7 patients for one year with denosumab, rather than with zoledronic acid, would be expected to prevent one additional SRE. In addition, a recent cost-effectiveness analysis using data from the pivotal phase III study of denosumab versus zoledronic acid in patients with breast cancer showed reductions in SREs and increased quality-adjusted life years (QALY) with denosumab. In patients with breast cancer and bone metastases, the cost per SRE avoided was $13,557 and the cost per QALY gained was $78,915, which is commonly considered good value in the United States (25).

The skeletal complications experienced by patients with advanced breast cancer and bone metastases often require aggressive management, including radiation to bone for treatment of pain and treatment or prevention of pathologic fractures. The less frequent use of radiation to bone with denosumab provides an objective measure of improved pain control in patients receiving denosumab and spares more patients the burden and expense of radiation therapy. The benefits of denosumab treatment for improved HRQoL were shown in a greater proportion of patients with clinically meaningful improvements in the FACT-G score, a specific measure of HRQoL, and greater relative overall FACT-G improvement with denosumab compared with zoledronic acid, regardless of pain severity at baseline.

A key difference between denosumab and zoledronic acid results from their distinct pharmacokinetic and pharmacodynamic profiles. Zoledronic acid is excreted intact primarily through the kidneys and has been associated with clinically significant deterioration in renal function (potentially including acute tubular necrosis and collapsing focal glomerulosclerosis) and renal failure in some patients (11, 26, 27). Denosumab elimination does not rely on renal function, as the antibody is metabolized through nonspecific catabolism in the reticuloendothelial system (28). The extent of renal impairment, therefore, has no effect on the pharmacokinetics or pharmacodynamics of denosumab (29). Renal deterioration in cancer patients is common, with many potential causes (30, 31). To manage the risk of renal toxicity, the zoledronic acid product labeling recommends renal monitoring with dose adjustment and/or withholding in case of renal impairment (11). An international expert panel recommended that nephrotoxic chemotherapy should not be administered on the same day as an intravenous bisphosphonate (7). These measures may impose an additional inconvenience on many patients, particularly those receiving other nephrotoxic therapies. Dosing of denosumab does not require renal monitoring or adjustment of dose or scheduling for renal function. In this study, per zoledronic acid labeling, patients with creatinine clearance less than 30 mL/minute at baseline were ineligible to enroll and zoledronic acid doses were adjusted or withheld for patients with impaired renal function (7, 11, 13). Nevertheless, 8.5% of patients treated with zoledronic acid experienced renal AEs, a rate similar to that reported in other studies (26). Conversely, the rate of renal AEs in denosumab-treated patients was lower than the background rate seen in placebo-group patients with metastatic cancer (23).

Acute-phase reactions are a documented side effect with zoledronic acid, but have not been attributed to denosumab based on 18 clinical trials involving more than 5,000 patients. These reactions seem to be transient immunedriven responses, usually following the first or second dose of intravenous bisphosphonates and commonly lasting from one to 3 days (32, 33). The flu-like symptoms associated with acute-phase reactions can be distressing and burdensome for patients; they may reduce patients’ overall HRQoL and potentially lead to early treatment discontinuation (34).

Another difference between denosumab and zoledronic acid is the route of administration. Denosumab is administered by subcutaneous injection, whereas zoledronic acid requires an intravenous infusion over at least 15 minutes (11, 32, 33). In a time-motion study, the median overall administration time associated with zoledronic acid infusion was 60 minutes for patients with breast cancer who did not receive chemotherapy (35). Subcutaneous administration provides additional convenience for patients and clinicians and eliminates the need for intravenous access, especially important for patients on hormonal or oral chemotherapies.

Advances in the treatment of breast cancer have increased survival for many patients, including those with metastatic disease. In recent studies, women with metastatic breast cancer had an estimated median survival ranging from 27 to 39 months (36, 37), underscoring the importance of managing patients’ overall health and well-being, including bone health and HRQoL. A 2009 international study of patients with metastatic cancer found that patients rated chronic pain as the most important HRQoL issue related to their disease, followed by difficulty in carrying out their usual tasks and worries about loss of independence and mobility (38). Prevention of SREs can have an important effect on patients’ freedom from pain, ability to maintain normal daily activities, and functional independence (2, 3, 5, 6). In summary, additional analyses from a large international phase III trial of patients with breast cancer and bone metastases provided additional evidence that denosumab was more efficacious than zoledronic acid in preventing or delaying SREs, radiation to bone, or hypercalcemia of malignancy, and in maintaining quality of life. Beyond these clinical benefits, treatment with denosumab also reduces the risks of renal toxicity and acute-phase reactions and provides the convenience of subcutaneous administration. Denosumab offers an efficacious and well-tolerated treatment option for preventing skeletal complications in patients with breast cancer and bone metastases.

Disclosure of Potential Conflicts of Interest

M. Martin has served as an advisor for Amgen and Novartis. R. Bell has served as an advisor for Amgen and Novartis. H. Bourgeois has served as an advisor for Amgen and Novartis. A. Britsky has served as an advisor and consultant for Amgen and Novartis and a speaker for Novartis. J. Diel has served as an advisor for and received honoraria from Roche, Amgen, and Novartis. A. Eniu has served as an advisor for Amgen and received a research grant from Novartis. L. Fallowfield has served as an advisor and consultant.
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### References


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