Original Article

Pain Outcomes in Patients With Advanced Breast Cancer and Bone Metastases

Results From a Randomized, Double-Blind Study of Denosumab and Zoledronic Acid

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BACKGROUND: In this study, the authors evaluated the effect of denosumab versus zoledronic acid (ZA) on pain in patients with advanced breast cancer and bone metastases. **METHODS:** The prevention of pain, reduction in pain interference with daily life activities, and the proportion of patients requiring strong opioid analgesics were assessed in a randomized, double-blind, double-dummy phase 3 study comparing denosumab with ZA for preventing skeletal-related events in 2046 patients who had breast cancer and bone metastases. Patients completed the Brief Pain Inventory-Short Form at baseline and monthly thereafter. **RESULTS:** Fewer patients who received denosumab reported a clinically meaningful worsening of pain severity (≥2-point increase) from baseline compared with patients who received ZA, and a trend was observed toward delayed time to pain worsening with denosumab versus ZA (denosumab, 8.5 months; ZA, 7.4 months; $P = .08$). In patients who had no/mild pain at baseline, a 4-month delay in progression to moderate/severe pain was observed with denosumab compared with ZA (9.7 months vs 5.8 months; $P = .002$). Denosumab delayed the time to increased pain interference by approximately 1 month compared with ZA (denosumab, 16.0 months; ZA, 14.9 months; $P = .09$). The time to pain improvement ($P = .72$) and the time to decreased pain interference ($P = .92$) were similar between the groups. Fewer denosumab-treated patients reported increased analgesic use from no/low use at baseline to strong opioid use. **CONCLUSIONS:** Denosumab demonstrated improved pain prevention and comparable pain palliation compared with ZA. In addition, fewer denosumab-treated patients shifted to strong opioid analgesic use. ***Cancer* 2013;119:832-8.** *© 2012 American Cancer Society.*

KEYWORDS: RANK ligand, denosumab, clinical trial, zoledronic acid, breast neoplasms, pain, analgesics.

INTRODUCTION

Pain is the most frequent consequence of bone metastases for patients with advanced cancer[1-3] and can significantly increase the emotional and physical burden of patients' disease. Conversely, patient time without moderate or severe pain has been associated with increased functionality and quality of life.[4,5] Therefore, avoiding and delaying the onset of significant pain for as long as possible is an important goal in the treatment of patients with cancer who have bone metastases. Randomized trials of bone-targeted agents primarily focus on the delay or prevention of skeletal-related events (SREs), such as pathologic fractures, surgery/radiotherapy to bone, or spinal cord compression. In those trials, pain was not counted as an SRE and may not have been optimally measured.

Previous studies have demonstrated that bisphosphonates can reduce skeletal complications and pain associated with bone metastases in patients with metastatic breast cancer and other types of solid tumors.[6-8] In addition, bisphosphonates may

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have the potential to improve patients' health-related quality of life.[9] However, to our knowledge, no studies to date have examined whether bisphosphonates lengthen the time until significant pain develops.

In a recently published, head-to-head phase 3 trial comparing the receptor activator of nuclear factor κB ligand (RANKL) monoclonal antibody denosumab (XGEVA; Amgen Inc., Thousand Oaks, Calif) with zoledronic acid (Zometa; Novartis, East Hanover, NJ), denosumab was superior in preventing SREs among patients with breast cancer and bone metastases.[10] Here, we report the effect of denosumab versus zoledronic acid on pain outcomes from that study, including pain severity, pain interference (ie, the degree to which pain interferes with common dimensions of feeling and function), and analgesic use.

MATERIALS AND METHODS

Study Design and Patients

This was an international, double-blind, double-dummy, active-controlled trial. Eligible adult patients had breast cancer and radiographic evidence of 1 or more bone metastases. Patients receiving or who had previously received intravenous or oral bisphosphonates for the treatment of bone metastases were excluded. The study duration from first patient enrolled to the primary analysis was approximately 34 months, and the median time on study was 17 months for patients in both arms. Comprehensive details of the trial design and methods have been previously published.[10] The study was approved by the Institutional Review Board or Ethics Committee for each site, and patients provided written, informed consent before enrollment. The study is registered with ClinicalTrials.gov as National Clinical Trial NCT00321464.

Randomization, Masking, and Treatment Schedule

Eligible patients were assigned randomly 1:1 to receive either a monthly subcutaneous injection of denosumab 120 mg and intravenous placebo or subcutaneous placebo and a monthly intravenous infusion of zoledronic acid 4 mg. Zoledronic acid dose adjustments for a creatinine clearance ≤60 mL/minute and withholding for rising creatinine levels were required according to the zoledronic acid (Zometa) prescribing information.[11]

Patient-Reported Outcomes Assessments

To portray the course of pain over the study period, pain severity and pain interference with daily functioning were assessed at baseline and at each monthly visit before study procedures or drug administration and continued either until the patient came off study or at the end of the randomized component of the study. Analgesic use also was recorded at each assessment.

TABLE 1. Analgesic Quantification Algorithm Score Categories

AQA Score	Description
0	No analgesic
1	Nonopioid analgesics
2	Weak opioids (ie, meperidine, codeine, tramadol)
3	Strong opioids ≤75 mg OME/d
4	Strong opioids >75-150 mg OME/d
5	Strong opioids >150-300 mg OME/d
6	Strong opioids >300-600 mg OME/d
7	Strong opioids >600 mg OME/d

Abbreviations: AQA, Analgesic Quantification Algorithm; OME, oral morphine equivalents; d, day.

Patients completed the Brief Pain Inventory-Short Form (BPI-SF) to assess pain severity and pain interference with daily functioning. The questionnaire consists of 11 items. Four items assess pain at its "worst," "least," "average," and "now," with the item "worst" used singly to represent pain severity in clinical trials. Seven items measure how much pain interfered with various daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep.[12]

The BPI-SF scores pain severity on a scale from 0 to 10, with 0 representing no pain and 10 representing "pain as bad as you can imagine." On the basis of prior research comparing pain severity ratings with reported pain interference, patients with scores from 1 to 4 were classified as having mild pain, patients who scored 5 or 6 were classified as having moderate pain, and patients who had scores from 7 to 10 were considered to have severe pain.[13] Worst-pain severity ratings also were dichotomized into a no or mild pain category (score, 0-4) and a moderate or severe pain category (score, 5-10).

The 7 items that measured pain interference with daily functioning also were scored on scale from 0 to 10, with 0 representing "no interference" and 10 representing "interferes completely." Subscale scores of pain interference with activity (interference with walking, general activity, and work) and affect (interference with relations with others, enjoyment of life, and mood), plus an aggregate or overall interference score (which included the subscales of activity and affect as well as sleep), were computed.[14]

Analgesic medication use was assessed using the 8-point Analgesic Quantification Algorithm (AQA).[15] AQA scores range from 0 to 7, in which 0 is no analgesic use and 7 is strong opioid use >600 mg oral morphine equivalents per day (Table 1).[15] A shift to strong opioid use (a change from ≤2 to 3 or higher on the AQA)

typically represents clinician awareness of a significant worsening of a patient's pain.

Pain Outcomes Assessed

Time-to-event and responder analyses were assessed for applicable pain outcomes. Pain endpoints included: 1) worsening or improvement in pain severity, as measured by the time to an increase or a decrease of $\geq$2 points in the pain severity score from baseline and the proportion of patients experiencing an increase or a decrease of $\geq$2 points in pain severity; 2) a delay in pain progression, as measured by the time to moderate or severe pain (score, >4 points) among patients who had no or mild pain (score, 0-4 points) at baseline and the proportion of patients experiencing moderate or severe pain among patients who had no or mild pain at baseline; 3) an increase or a decrease in pain interference, as measured by the time to an increase or a decrease of $\geq$2 points in the pain interference score from baseline; 4) the time to an increase of $\geq$2 points in pain interference among patients who had no or mild pain at baseline; and 5) increased analgesic use, as measured by the time to use of strong opioid analgesics and the proportion of patients requiring strong opioids. Subgroup analyses also were conducted to evaluate pain severity and pain interference among patients who had no or mild pain at baseline and to evaluate the palliation of pain among patients who had moderate or severe pain at baseline.

Minimally Important Difference

The minimally important difference (MID) is the smallest difference in a patient-reported outcome measure that patients are likely to perceive as beneficial or detrimental.[16] A common, distribution-based approach to determining the MID is to use one-half of the standard deviation (SD) for the measure.[17] One-half of the SD for worst pain at baseline was 1.5 for all patients, and half of the SD for pain interference at baseline was 1.3 for all patients. To be conservative, we rounded up to 2 points for the MID estimate for both scales. Thus, a meaningful improvement or worsening in pain severity or pain interference was defined as a change of $\geq$2 points. This MID estimate is in agreement with previously published MID data for the BPI-SF worst pain score, which was calculated using both anchor-based and distribution-based methods in a population of patients with advanced breast cancer and bone metastases.[18]

Statistical Analyses

Analyses were conducted on all randomized patients who had at least 1 patient-reported outcome assessment. Analyses of increases or decreases of $\geq$2 points on the BPI-SF were based on the risk set (ie, including patients who could achieve the respective change based on their baseline value). Responder analyses were performed through month 18, when $\geq$30% of patients had discontinued because of death, disease progression, or withdrawal of consent. Details on patient discontinuation were previously published.[10]

Kaplan-Meier estimates were generated for the time-to-event endpoints. Hazard ratios (HRs) and associated, 2-sided 95% confidence intervals (CIs) were estimated using a proportional-hazards model stratified according to the stratification factors and adjusted by covariates. The time-to-event was defined as the time interval from the randomization date to the date of the first observation of the outcome of interest. Patients who had not achieved the outcome were censored at their last assessment.

Responder analysis was used to determine the proportion of patients with pain worsening and improvement by study visit. The chi-square was used to compare proportions between treatment groups. A primary method of imputation was applied for all missing data for the responder analysis. If there were observations before and after the missing response, then the average of the 2 neighboring responses was used to obtain an imputed value. If there was no observation before the missing response, then the last observation was carried backward. Missing baseline observations before study drug administration were not imputed using on-study observations. If there was no observation after the missing response, then the worst outcome was assumed and applied. For example, for pain interference with activity questions, if the responder criterion was an increase of $\geq$2 points (increased pain interference), then an increase of at least 2 points from baseline was imputed. Conversely, if the responder criterion was a decrease of $\geq$2 points (decreased pain interference), then the least favorable scenario of a decrease of <2 points from baseline was imputed. Multiple imputation was used for additional sensitivity analyses.

The time to experiencing a score $\geq$3 (strong opioid use) on the AQA was evaluated by treatment group among patients who had a score $\leq$2 (no analgesics, nonopioid analgesic, or weak opioid use) at baseline. The proportion of patients reporting use of strong opioid analgesics (AQA score, $\geq$3) on study was determined for patients who had no or low analgesic use (AQA score, $\leq$2) at baseline.

RESULTS

Patient Characteristics

The study enrolled 2046 patients (denosumab arm, 1026 patients; zoledronic acid arm, 1020 patients) between April 2006 and December 2007. Demographic and clinical characteristics at baseline were comparable between

TABLE 2. Baseline Characteristics

Characteristic	Zoledronic Acid, N = 1020	Denosumab, N = 1026
Women, n (%)	1011 (99)	1018 (99)
Median age, y	56	57
ECOG status of 0 or 1, n (%)	932 (91)	955 (93)
Positive hormone receptor status, n (%)	726 (71)	740 (72)
Median time from initial diagnosis of bone metastases to randomization, mo	2	2
Previous SRE[a], n (%)	373 (37)	378 (37)
Prior oral bisphosphonate use[a], n (%)	38 (4)	42 (4)
Presence of visceral metastases, n (%)	525 (51)	552 (54)
Pain interference score: Mean ± SD		
Activity score	3.5 ± 3.0	3.4 ± 3.0
Affect score	2.8 ± 2.7	2.8 ± 2.8
Aggregate score	3.1 ± 2.6	3.1 ± 2.7
Worst pain severity score		
Mean ± SD	4.2 ± 2.8	4.1 ± 2.9
No. evaluable/total (%)		
0: No pain[b]	140/951 (15)	145/975 (15)
1-4: Mild pain[b]	360/951 (38)	397/975 (41)
5-6: Moderate pain[b]	215/951 (23)	208/975 (21)
7-10: Severe pain[b]	236/951 (25)	225/975 (23)
Analgesic use score, n (%)		
0-2: No or low analgesic use	848 (83)	863 (84)
3-7: Strong opioid use	172 (17)	163 (16)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; SRE, skeletal-related event.
[a] Based on randomization.
[b] Based on observed data.

the 2 treatment groups (Table 2). Patients were diagnosed with bone metastases a median of 2 months before randomization, and most patients were hormone receptor-positive (71%-72%). Despite the short period between diagnosis of metastatic bone disease and study enrollment, approximately 33% of patients already had experienced an SRE. The median time on study was 17 months for both treatment groups. Reasons for discontinuation were comparable between treatment groups. The most common reasons for discontinuation, regardless of treatment, were death, disease progression, and withdrawal of consent. Primary efficacy and safety data, along with details on study discontinuation, have been reported previously.[10]

Approximately 53% of patients (n = 542) in the denosumab group and 49% of patients (n = 499) in the zoledronic acid group reported no or mild pain at baseline and were at risk for developing increased pain over time. Among these patients, the mean ± SD worst pain severity scores for the denosumab and zoledronic acid groups were 1.4 ± 1.1 and 1.4 ± 1.2, respectively; and the mean ± SD pain interference scores were 1.8 ± 2.1 and 1.7 ± 1.9, respectively. No or low (score, 0-2) analgesic use was reported by 92.1% of patients who received denosumab and 90% of patients who received zoledronic acid.

Figure 1. Pain prevention is illustrated according to the proportion of patients that shifted from no pain or mild pain at baseline to moderate pain or severe pain on-study.

Pain Severity

Worsening pain severity, as measured as the mean ± SD change from baseline, was observed throughout the study. The proportion of patients with no or mild pain at baseline who experienced worsening of pain to moderate or severe on study increased from 19% at month 1 to 57% at month 18 among all patients combined. Also, 43% of patients reported moderate or severe pain at baseline, yet only approximately 16% were using strong opioids (AQA score, ≥3) at baseline.

At the majority of time points, fewer denosumab-treated patients experienced meaningful worsening of pain severity (≥2-point increase from baseline) than zoledronic acid-treated patients (mean relative difference between denosumab and zoledronic acid over the study period, 7%; absolute difference, 3%; denosumab, n = 975; zoledronic acid, n = 951). A trend toward a delay in the median time to an increase of ≥2 points in pain severity was observed with denosumab (8.5 months; n = 901) compared with zoledronic acid (7.4 months; n = 892; HR, 0.90; 95% CI, 0.80-1.01; $P = .08$).

Pain worsening among patients who had no or mild pain at baseline to moderate or severe pain on study was assessed (denosumab, n = 542; zoledronic acid, n = 500). Fewer patients who received denosumab progressed from no or mild pain to moderate or severe pain compared with zoledronic acid (relative difference, 15%; absolute difference, 5%) (Fig. 1), with an almost 4-month delay in the median time to pain worsening to moderate or severe with denosumab compared with zoledronic acid ($P = .002$) (Fig. 2).

Palliation of pain severity, as measured by the proportion of patients with meaningful improvement (a decreased ≥2 points) in worst pain score, was similar between treatment groups, ranging from 26% at 1 month to 16% at 18 months for denosumab (n = 975) and from 26% at 1 month to 18% at 18 months for zoledronic acid (n = 951). The median time to meaningful improvement in the worst pain score also was similar between treatment arms in both the full group of patients (denosumab [n = 747], 2.7 months; zoledronic acid [n = 745], 2.8 months; HR, 1.02; 95% CI, 0.91-1.15; $P = .72$) and in the subgroup of patients who had moderate or severe pain at baseline (denosumab [n = 433], 1.9 months; zoledronic acid [n = 452], 1.9 months; HR, 0.97; 95% CI, 0.84-1.12; $P = .68$).

Figure 2. Pain prevention is illustrated according to the time to moderate pain or severe worst pain (scores >4) among patients who had no pain or mild pain at baseline (scores from 0 to 4). KM indicates Kaplan-Meier; HR, hazard ratio; CI, confidence interval.

Pain Interference

A numeric difference in the time to an increase in aggregate pain interference of ≥2 points from baseline was observed with denosumab compared with zoledronic acid (denosumab, 16.0 months; zoledronic acid, 14.9 months; HR, 0.89; 95% CI, 0.78-1.02; $P = .09$) among all patients at risk, with comparable results observed for pain interference with activity and affect.

Among patients who had no or mild pain at baseline, a trend toward a longer time to increased pain interference also was observed with denosumab compared with zoledronic acid for all 3 pain-interference measures: pain interference with activity, pain interference with affect, and aggregate pain interference (Fig. 3).

The time to a meaningful decrease in aggregate pain interference of ≥2 points from baseline was similar between treatment groups (denosumab: median, 2.9 months; zoledronic acid: 3.2 months; HR, 0.99; 95% CI, 0.86-1.15; $P = .92$), and comparable results were observed for pain interference with activity and with affect.

Figure 4. The proportion of patients who shifted from no or low analgesic use to strong opioid use is illustrated.

Figure 3. (A-C) The time to increased (≥2-points from baseline) pain interference is illustrated among patients who had no pain or mild pain at baseline. KM indicates Kaplan-Meier; HR, hazard ratio; CI, confidence interval.

Analgesic Score

Fewer patients in the denosumab arm shifted from no or low analgesic use (AQA scores, 0-2) to strong opioid analgesic use (AQA scores, 3-7) compared with patients in the zoledronic acid arm (relative difference, 20%; absolute difference, 2%) (Fig. 4). Among patients who had no or low analgesic use at baseline, the median time to strong opioid analgesic use was not reached in the denosumab arm, and it was 29.5 months in the zoledronic acid arm (HR, 0.90; 95% CI, 0.75-1.08; $P = .27$).

DISCUSSION

Patients with cancer fear pain more than any other symptom;[19,20] thus, delaying the onset of pain is an important treatment outcome from a patient's perspective. The time to pain worsening and the time to first use of strong opioid-type analgesic drugs represent meaningful endpoints for patients but rarely are reported in clinical trials of cancer. Keeping pain in the mild range has been associated with significantly better function and quality of life.[13,21]

In the current study, the majority of patients who started the study with no or mild pain experienced pain worsening to moderate or greater severity, as would be expected in an advanced cancer population over 18 months. It is noteworthy that fewer patients in the denosumab arm had worsening of pain severity at the majority of time points compared with patients in the zoledronic acid arm. The proportion of patients achieving a significant reduction in pain on study was similar between treatment arms at approximately 2 months. Responder analysis results were consistent across primary and multiple imputations and using observed data.

Denosumab also significantly extended the amount of time that patients who had no or mild pain at baseline remained without moderate or severe pain by a median of almost 4 months compared with zoledronic acid. Similarly, denosumab delayed worsening in pain-related interference with daily feeling and function by a median of greater than 4 months compared with zoledronic acid, although the difference was not statistically significant. A lower proportion of patients who were receiving denosumab shifted from no or low analgesic use to strong opioid analgesic use compared with patients who were receiving zoledronic acid (overall relative reduction, 20% with denosumab compared with zoledronic acid).

These data illustrate the high burden of pain among patients with bone metastases secondary to breast cancer and indicate that patient-reported levels of pain do not necessarily correspond with matching levels of analgesic use. At baseline, 50% of patients in each treatment group reported moderate to severe pain, but <20% reported using strong opioid analgesics. This discrepancy between patient-reported pain and documented analgesic use was observed throughout the study. For example, among patients who had no or mild pain at baseline, 57% to 66% reported progression to moderate or severe pain by study end; yet, among those who had no or low analgesic use at baseline, only 26% to 29% reported strong opioid use on study. This observation has been reported consistently in other studies.[22-24] Additional research can help to determine whether strong opioid use is low in these patients because of physician under-treatment of pain, under-reporting of pain by patients to physicians, patient or physician fear of opioid-related side effects, or a combination of these factors.

It is believed that bone pain occurs from increasing bone resorption and acidification of the bone tumor microenvironment from active osteoclasts.[25-27] Because both denosumab and zoledronic acid inhibit osteoclast function, they appear to have similar effects on pain palliation. The greater effect of denosumab over zoledronic acid on preventing the worsening of pain may be explained by its greater ability to inhibit osteoclast formation and function, thereby suppressing cancer-induced bone destruction.

A limitation of these analyses is that no period of stable bone pain was required or evaluated before the start of treatment, which could pose difficulty in attributing changes in pain to treatment. However, possible differences in stable bone pain before treatment were offset by the large sample size and the randomized nature of this trial. In addition, the potential benefits to daily activities of subcutaneous delivery of denosumab over intravenous administration of the comparator, zoledronic acid, were not captured, because both treatment arms received subcutaneous and intravenous administration.

In conclusion, denosumab was more effective at extending the time to significant increases in pain and pain-related functional interference as well as the time to first use of strong opioid analgesics compared with zoledronic acid, particularly among patients who had no or mild pain at baseline. These patient outcomes may be of particular relevance to patients with breast cancer who are newly diagnosed with bone metastases, as patients were enrolled in this study a median of 2 months after their diagnosis of bone metastases. These findings also illustrate the natural progression of pain in patients with metastatic breast cancer, which interferes with their ability to function and requires careful medical management.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Cleeland, Dr. Fallowfield, and Dr. Patrick have been consultants/speakers for and received honorarium from Amgen. Dr. Body has been a consultant/speaker for Amgen and Novartis and an advisory board member for Amgen. Dr. Stopeck has been a consultant/speaker for Amgen and Novartis and received honoraria/research funding from Amgen. Dr. von Moos has been a consultant to Amgen, Roche, and Novartis and a speaker for Amgen and Roche. Ms. Mathias has been a consultant to and received honorarium from Amgen. Dr. Clemons has received research funding from Amgen and has been a consultant/speaker for and received honorarium from Amgen and Novartis. Dr. Tonkin and Dr. Masuda have received research funding from Amgen. Dr. Lipton has been a consultant/speaker for and received honoraria/research funding from Amgen and Novartis and has provided expert testimony for Novartis. Dr. de Boer has served on the advisory board for and received research funding from Amgen. Dr. Qian, Dr. Jiang, Dr. Dansey, Dr. Braun, and Dr. Chung are employees of and receive stock/stock options from Amgen.

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