Effect of zoledronic acid on pain associated with bone metastasis in patients with prostate cancer

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Background: Zoledronic acid reduces skeletal-related events associated with prostate cancer and has long-term efficacy in pain outcomes. Findings of treatment group differences in pain early in treatment are less reliable. We used a recently recommended analytic approach to examine the effect of zoledronic acid on pain.

Materials and methods: In a trial of zoledronic acid (n = 214) versus placebo (n = 208), we used the Brief Pain Inventory to assess pain at baseline, 3 weeks, 6 weeks and every 6 weeks thereafter for a total of 60 weeks. We used a modified longitudinal rank test to determine whether clinically meaningful changes in pain were related to treatment group.

Results: Seventy-six of 214 patients (35.5%) receiving zoledronic acid and 62 of 208 patients (29.8%) receiving placebo completed the 60-week visit (P = 0.22). In all 11 pain assessments, patients receiving zoledronic acid reported more favorable, clinically meaningful changes in pain scores. Overall, patients receiving zoledronic acid had a 33% chance of a favorable response, compared with 25% for patients receiving placebo (P = 0.04; 95% CI 0.5% to 15.6%).

Conclusions: Zoledronic acid was more likely than placebo to be associated with clinically meaningful reductions in pain. Thus, zoledronic acid may help to avert the pain experienced by patients with progressing metastatic disease secondary to prostate cancer.

Key words: antineoplastic agents, bone neoplasms, diphosphonates, pain, prostatic neoplasms, research design

introduction

Bisphosphonates have been used successfully to prevent skeletal morbidities in metastatic cancer [1]. At present, the only bisphosphonate approved for the prevention of skeletal morbidities due to metastatic prostate cancer is zoledronic acid (Zometa, Novartis Pharmaceuticals Corporation). Compared with placebo, zoledronic acid has been shown to reduce the number and rate of skeletal-related morbidities and to increase the time until patients’ first skeletal-related morbidity [2, 3]. A recent analysis of clinical trial data for 24 months after randomization demonstrated significantly better pain responses towards the end of the study for patients receiving zoledronic acid than for those receiving placebo [3]. However, consistent treatment group differences were not detected during the first 15 months of the trial [2], calling into question the short-term efficacy of zoledronic acid in relieving pain. Using an analytic approach that has been recognized recently as more appropriate for pain trials, we re-examined the effect of zoledronic acid on pain among men with prostate cancer metastatic to bone during the first 15 months of treatment.

Many clinical trials evaluating pain outcomes have relied on between-group comparisons or mean change-from-baseline scores on a continuous measure of pain. A recent Cochrane review [4] of bisphosphonates for the relief of pain secondary to bone metastases recommended against the use of mean pain scores, which was the methodology applied in the analysis by Saad et al. [2, 3], suggesting instead that investigators examine the proportions of patients with pain relief. This recommendation is consistent with assertions by Farrar [5] and Guyatt et al. [6] that comparing proportions of responders between groups provides findings with greater clinical relevance. Accordingly, we modified a standard statistical method to examine differences over time between zoledronic acid and placebo in the occurrence of clinically meaningful changes in pain.

materials and methods

The clinical trial was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 136 centers in 17 countries in Australasia, Europe, North America and South America [2]. The trial population consisted of 643 patients with prostate cancer who were stratified upon entry according to the presence or absence of distant metastases at initial diagnosis. Patients received a 15-min intravenous infusion of either 4 mg of zoledronic acid (n = 214), 8 mg of zoledronic acid (n = 221), or
placebo ($n = 208$) every 3 weeks for 15 months, in addition to antineoplastic therapy. A protocol amendment switched all patients assigned to the 8 mg zoledronic acid group to a dosage of 4 mg due to concerns regarding renal safety. Since this 8/4 mg group does not correspond to any regimen patients can receive today in practice, we omitted this arm from the analysis, leaving 422 total patients. The present study was approved by the institutional review board of Duke University Medical Center.

Basic demographic variables were collected at randomization, along with clinical variables including date of cancer diagnosis, site and date of metastases other than bone at initial diagnosis, primary site of cancer, history of skeletal morbidities prior to study entry, serum creatinine level, prostate-specific antigen, and baseline Eastern Cooperative Oncology Group (ECOG) performance status. Occurrence of a skeletal-related morbidity was recorded at each clinic visit and was defined as radiation to bone, pathologic fracture (vertebral or non-vertebral), spinal cord compression, surgery to bone, or change in antineoplastic therapy to treat bone pain. For additional details regarding study design, see Saad et al. [2].

**Brief Pain Inventory**

In the original clinical trial protocol, pain intensity was defined *a priori* as the primary efficacy variable for the patient-reported outcome assessments. Pain intensity was measured using a composite score from the Brief Pain Inventory (BPI) [7] that took the average of each patient’s ratings of worst pain, least pain, average pain and current pain (each reported on a 0–10 scale, with 10 indicating greatest pain). The BPI has been validated in several countries [7–9]. Patients completed the questionnaire at baseline, months 1 and 2, and every other month thereafter up to month 24. The BPI was administered in person before the patient was interviewed by the physician or received study medication.

**statistical analysis**

We used chi-square tests to compare the proportion of patients completing the 60-week BPI assessment in each treatment group, and we used log-rank tests to compare mortality during the study period in each group. Statistical significance was determined using a two-sided $\alpha = 0.05$ level.

To compare the treatment groups with respect to BPI scores over time, we used a modified version of a standard multivariate non-parametric statistic [10, 11]. Non-parametric tests are often used for analyzing patient-reported outcomes such as pain, because these outcomes frequently have skewed distributions that are unsuitable for parametric tests (e.g., analysis of covariance). In a standard non-parametric analysis, such as the Mann–Whitney test (also known as the Wilcoxon rank sum test), one compares ranks of scores rather than the raw scores themselves. Our modification of this approach makes the test more conservative by requiring that one patient can be ranked higher than another patient only when their scores differ by some clinically significant amount. For 11-point pain scales such as the BPI, a two-point difference is generally considered clinically significant [12, 13].

Specifically, we computed change-from-baseline scores for the BPI for each patient for each time point. For each time point, we determined the proportion of cases in which a patient in the zoledronic acid group had a more favorable pain response than a patient in the placebo group (placebo change-from-baseline score minus zoledronic acid change-from-baseline score $\geq 2$). If a patient in one group was dead and the corresponding patient in the other group was alive, we considered the living patient to have had a more favorable response, regardless of his or her BPI score [14]. We calculated a similar proportion of favorable responses for patients in the placebo group and plotted the proportions of favorable responses over time. The outcome of interest is the overall difference between the proportions of favorable responses for the zoledronic acid and placebo groups. We used a non-parametric, longitudinal rank test to compare the overall difference in these proportions over the duration of the trial [15], and we used the non-parametric bootstrap method with 1000 samples to generate a 95% confidence interval (CI) for the overall difference in proportions [16]. The resulting estimator is a multivariate generalization of the Mann–Whitney statistic.

We handled missing BPI responses using an algorithm described by Engels and Diehr [17]. When a BPI assessment was available immediately before and after the missing response, we took the average of the two neighboring responses to obtain the imputed value. If a response at the immediately preceding visit was not available, the next-observation-carried-backward method was used. We imputed missing values due to dropout using the last-observation-carried-forward method. This approach has been shown to yield less bias and variance than other single-imputation methods [17].

We performed three sensitivity analyses to determine the effects of varying the criteria for a favorable response and of assuming that dropout due to death occurred at random: (1) same analysis as above, but treating data for patients who had died as missing after the date of death [18]; (2) same analysis as above, but using any difference in BPI scores (instead of a two-point difference) as the criterion for counting favorable comparisons among treatment and control patients; and (3) same as the second sensitivity analysis, but treating data for patients who had died as missing after the date of death. We conducted a fourth sensitivity analysis to determine whether the treatment effect would differ if the sample was restricted to patients whose baseline BPI score was greater than zero.

**results**

Table 1 shows the baseline characteristics of the patients by treatment group. Seventy-six of the 214 patients (35.5%) randomized to zoledronic acid and 62 of the 208 patients (29.8%) randomized to placebo completed the 60-week BPI assessment ($P = 0.22$). The 1-year survival rate was 85.2% for the zoledronic acid group and 78.3% for the placebo group ($P = 0.21$).

Figure 1 shows the differences between groups in terms of the likelihood of a favorable pain response. At all 11 assessment times, patients randomized to zoledronic acid reported more favorable pain responses compared with patients receiving

| Table 1. Baseline characteristics of patients by treatment group |
|------------------|------------------|
| **Characteristic** | **Treatment group** | **Placebo** |
|                  | **Zoledronic acid** | **Placebo** |
|                  | ($n = 214$) | ($n = 208$) |
| Age, mean (SD), years | 71.8 (7.9) | 72.2 (7.9) |
| Race, n (%) | | |
| Caucasian | 178 (83) | 173 (83) |
| Black | 24 (11) | 19 (9) |
| Other | 12 (6) | 17 (8) |
| ECOG status, n (%) | | |
| 0 | 85 (39.7) | 93 (44.7) |
| 1 | 112 (52.3) | 97 (46.6) |
| 2 | 17 (7.9) | 18 (8.7) |
| Bone metastases, mean (SD), n | 4.2 (2.5) | 4.2 (2.6) |
| Time since diagnosis, months | | |
| Mean (SD) | 62.2 (43.5) | 66.6 (46.9) |
| Median | 51.8 | 56.9 |
| Brief Pain Inventory score, mean (SD) | 2.0 (2.0) | 2.1 (2.0) |
placebo. Over the duration of the trial, a typical zoledronic acid patient had a 33% chance of having a favorable response, compared with a typical placebo patient, who had a 25% chance of a favorable response—a difference that was statistically significant ($P = 0.036; 95\% \text{ CI} 0.5–15.6$).

Sensitivity analyses showed that the superiority of the zoledronic acid group relative to placebo was consistent across variations in the definition of clinically meaningful change and the way in which deaths were incorporated into the analysis. Differences in the likelihood of favorable response for zoledronic acid compared with placebo ranged from 6.7% to 8.8%. Limiting the sample to patients who had some baseline pain ($\text{BPI} > 0$) increased the difference in favorable response rates to 8.4% ($95\% \text{ CI} –0.6$ to 15.1). The increase in the confidence interval is probably due to reducing the sample size ($n = 140$ for the zoledronic acid group, $n = 140$ for the placebo group).

**discussion**

Zoledronic acid has been shown to prevent or delay skeletal-related morbidities due to bone metastases associated with prostate cancer. Using an analytic technique that characterizes pain outcomes according to the overall likelihood of each treatment group to experience a favorable response, we found consistently superior pain outcomes for patients receiving zoledronic acid throughout the first 15 months of the trial. Together with the results of the 24-month analysis reported by Saad et al. [3], our findings indicate that patients with metastatic prostate cancer experienced clinically significant levels of pain relief throughout the course of treatment.

Our findings must be interpreted in the context of a design limitation from the original Saad et al. [2] study. Whereas skeletal-related morbidities were recorded continuously throughout the trial, pain assessments were conducted at fixed time points approximately 90 days apart. Thus, it is likely that some morbidities developed and resolved between pain assessments, making it difficult to examine all experiences of pain associated with the disease. This limitation was noted by Weinfurt et al. [19] when they discussed the significant effect of skeletal morbidities on health-related quality of life (HRQOL) without detectable treatment group differences in HRQOL, even though treatment differences in skeletal morbidities exist.

A second limitation of our analysis is that it relied only on BPI scores to record pain, ignoring the fact that the occurrence of pain is necessarily part of the definition of many of the skeletal-related morbidities comprising the primary clinical end point (e.g. radiation or surgery to bone to treat bone pain). Due to the spacing of the BPI assessments, it is possible that acute pain occurred and was resolved by radiation or surgery between BPI assessments. Thus, a more realistic picture of the painful experiences averted would combine the BPI results with the pain-related skeletal morbidities. It was not possible for us to do this, however, because we could not eliminate the possibility of double-counting painful events. Therefore, our estimate of the effect of zoledronic acid on pain should be considered a lower bound.

Prostate cancer metastatic to bone results in painful and burdensome skeletal-related morbidities. Previous research has demonstrated that zoledronic acid reduces the likelihood that such morbidities will occur. The findings of the present study suggest that patients receiving zoledronic acid experienced a higher likelihood of clinically meaningful reductions in pain, compared with patients receiving placebo. Thus, zoledronic acid may help to avert the pain experienced by patients with progressing metastatic disease secondary to prostate cancer.

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**references**