Published in final edited form as:

Cancer. 2008 September 15; 113(6): 1438–1445. doi:10.1002/cncr.23775.

Zoledronic Acid and Skeletal Complications in Patients With Solid Tumors and Bone Metastases:

Analysis of a National Medical Claims Database

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Abstract

BACKGROUND—Bone is among the most common sites of metastasis in patients with advanced cancer, and the development of bone metastases places patients at increased risk for skeletal complications.

METHODS—This retrospective claims analysis included only patients with a diagnosis of bone metastasis who had a single type of solid tumor of the breast (women), prostate, or lung and experienced ≥ 1 skeletal complication between January 2002 and October 2005.

RESULTS—The mean follow-up ($\pm$ standard deviation) for zoledronic acid (ZA)-treated patients versus untreated patients was 12.2 ± 9.05 months versus 8.7 ± 9.28 months, respectively ($P < .001$). The monthly rate of skeletal complications in ZA-treated patients versus untreated patients was 0.29 ± 0.3 per month versus 0.43 ± 0.4 per month, respectively ($P < .001$). Persistent ZA use was associated with longer follow-up duration ($P < .05$) and a greater probability of continuing follow-up. Greater persistency was associated with lower monthly rates of skeletal complications ($P < .05$). The length of follow-up for ZA use according to the recommended dosing schedule was 17.11 months compared with 9.93 months for nonrecommended schedules and 8.68 months for no treatment (analysis of variance; $P < .001$). The rate of skeletal complications with ZA use on the recommended schedule was 0.16 events per month versus 0.31 events per month for nonrecommended schedules and 0.43 events per month for no treatment. In the subgroup analysis, the mean time to first complication was 185 ± 210 days in the ZA-treated group versus 98 ± 161 days in the untreated group ($P < .0001$). The mean time from the first complication to the second complication was 111 ± 124 days in the ZA-treated group versus 86 ± 114 days in the untreated group ($P < .05$).

CONCLUSIONS—Real-world evidence indicated that ZA reduced the skeletal morbidity rate and delayed the time to skeletal complications.

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Allan Lipton has provided expert testimony to Novartis and serves on its speakers bureau and advisory board.

This study was conducted using a licensed data set from PharMetrics to Novartis Pharmaceuticals.

Keywords

zoledronic acid; skeletal complications; retrospective claims analysis; persistency; bone; cancer

Bone is among the most common site of metastasis in advanced cancer, and bone metastases occur in approximately 65% to 75% of patients who have metastatic prostate cancer or breast cancer and in approximately 30% to 40% of patients who have metastatic lung cancer.¹ The development of bone metastases places patients at risk for skeletal complications (eg, pathologic fractures, spinal cord compression, severe bone pain) and the need for surgery or radiation to the bone.^{1,2} Skeletal complications are recurrent events over the course of the disease. For instance, in patients with advanced breast cancer, on average, a skeletal event is experienced every 3 to 4 months.²

Skeletal complications can have devastating effects on patients' daily lives. These events are associated with substantial morbidity (eg, bone pain, limited mobility, diminished quality of life) and reduced survival.^{1,3} In patients with breast cancer, survival is related inversely to the number of bone metastases. Patients with ≥ 3 bone lesions have a shorter survival than patients with fewer lesions.⁴ Preventing the development, reducing the rate of occurrence, and delaying the onset of skeletal complications are essential for reducing morbidity and sustaining patients' functional independence.

Skeletal complications increase resource use and costs.^{1,3} The management of complications because of metastatic bone disease has been identified as the largest single contributor to hospital costs in patients with breast cancer.⁵ In 1 study that analyzed hospital admissions between 1987 and 1989, the average cost for bone disease-related admission (in US dollars) was \$12,407. Radiation therapy contributed significantly to the total cost, at an average of \$6750 per patient (from the diagnosis of bone metastasis until death). These costs may be conservative, because that analysis did not include physician or surgeon fees, charges for outpatient chemotherapy or analgesics, or lost days of productivity.⁵

In a retrospective analysis using data collected between 1995 and 2002 on 534 patients from a large US health insurance claims database, the lifetime skeletal event cost per patient with lung cancer and bone metastases was estimated at approximately \$12,000.³ In that analysis, radiotherapy accounted for the greatest proportion of cost (60%) per skeletal event type, followed by bone surgery (21%), treatment of fractures (15%), and other skeletal events (4%). Those investigators observed that approximately 80% of the costs of treatment were incurred within 2 months of the first skeletal event claim, indicating that early intervention may reduce morbidity and associated costs.

A recently conducted study estimated the direct medical costs associated with diagnosed metastatic bone disease in the United States. Data were derived from employer-paid commercial or Medicare supplemental insurance plans that covered approximately 14 million individuals of all ages during the years 2000 through 2004. Cost assessments included inpatient, outpatient, and pharmaceutical drug claims. Estimates of direct costs for 4190 cancer patients with metastatic bone disease (cases) were compared with estimates for 4190 cancer patients without metastatic bone disease (controls). Primary cancer of the lung, breast, and prostate constituted 25%, 18%, and 12% of the patient sample, respectively. Patients were followed for a mean of 21 months.⁶ Compared with controls, the mean monthly incremental costs were \$24,946 higher for patients with lung cancer ($P < .001$), \$40,276 higher for patients with prostate cancer ($P < .001$), and \$63,455 higher for patients with breast cancer ($P < .001$). Outpatient expenditures represented the largest cost differential between cases and controls.⁶

Bisphosphonates play an indisputable role in preventing skeletal complications secondary to bone metastases, reducing their rate of occurrence, and delaying their onset.² Tumor cells in bone marrow secrete paracrine factors that stimulate osteoclasts, leading to osteolysis and consequent disruption of normal bone metabolism. Bisphosphonates act by accumulating in the resorption lacunae, where they are internalized by osteoclasts and disrupt the biochemical processes required for bone resorption. Bisphosphonates also have a direct apoptotic effect on osteoclasts and may have a similar direct effect on tumor cells.^{2,7}

Bisphosphonates have demonstrated efficacy in reducing skeletal complications related to metastatic bone lesions in a range of solid tumor types, including breast, prostate, and lung cancers.⁸ In breast cancer, for instance, bisphosphonate therapy has been associated with fewer skeletal-related events, a delay in the occurrence of events, reduced pain and analgesic consumption, and improved quality of life.² Consequently, these agents are considered an important component of the overall management strategy for malignant bone disease and its prevention. The American Society of Clinical Oncology treatment guidelines recommend the use of intravenous bisphosphonates at first radiographic evidence of osteolytic bone destruction in patients with breast cancer.⁹

Zoledronic acid (ZA; Zometa, Novartis Pharmaceuticals, Florham Park, NJ), the most potent bisphosphonate,² has an established efficacy profile in patients with breast, prostate, and lung cancer as well as in patients with multiple myeloma.^{10–13} In clinical trials, ZA use reduced the proportion of patients that experienced skeletal complications over the study periods, prolonged the time to first skeletal complication, and reduced the annualized number of skeletal events compared with placebo.^{10–12} To provide evidence on the impact of ZA treatment on the health of cancer patients with bone metastases in the real-world treatment setting, we conducted an outcome study using a nationally representative claims database.

MATERIALS AND METHODS

Study Design

This was a retrospective claims analysis study using data from the PharMetrics integrated claims database, a nationally representative database of medical and pharmaceutical claims that contains 80 US health plans and covers 55 million patients. PharMetrics captures data on prescriptions, office visits, hospital stays, procedures, and diagnostic tests. PharMetrics datasets are structured to protect patients' identity and are in compliance with the Health Insurance Portability and Accountability Act of 1996. PharMetrics datasets do not contain patients' names. Rather, patients are given a unique identifying numbers to enable the conduct of research like that reported in this article.

Included in this study were patients who had a single type of solid cancer tumor of the breast (women), prostate, or lung, who were diagnosed with bone metastasis, and who experienced ≥ 1 skeletal complications (before or after receiving ZA) between January 2002 and October 2005. Patients must have been enrolled in the plan for at least 6 months before their initial diagnosis of bone metastasis. Excluded were patients who had cancers other than breast, prostate, or lung and patients who had multiple cancers. Also excluded were patients who had received any type of bisphosphonate other than ZA.

Patients were stratified into 2 groups: *untreated* (patients who had no exposure to intravenous bisphosphonate of any type during the study) and *ZA-treated* (patients who received ZA during the study). On the basis of the dates retrieved from claims data, several chronologic patterns of clinical events were identified, including the following: bone metastasis→ZA use→skeletal complication; skeletal complication→ZA use→bone metastasis; same date for skeletal complication and bone metastasis→ZA use; same date for skeletal complication, bone

metastasis, and ZA use; bone metastasis→ZA use and skeletal complication on the same day; skeletal complication→bone metastasis, no ZA use.

A subpopulation of patients who did not experience any skeletal complications before ZA treatment was also identified to assess the relation between the initiation of ZA treatment and the time from bone metastasis to the first and subsequent skeletal complications. Patients in this subgroup met 1 of the following 3 chronologic patterns of clinical events: bone metastasis→ZA use→skeletal complication (ZA-treated group); same date for bone metastasis and ZA use→skeletal complications (ZA-treated group); bone metastasis→skeletal complication, no ZA use (untreated group).

Study Endpoints

We evaluated the following study endpoints: the relation between ZA use and no intravenous bisphosphonate treatment and length of follow-up from metastasis to the last claim in the dataset; the association between ZA use and change in the rate of initial and subsequent monthly rates of skeletal complications; the relation between ZA initiation and the time to first and subsequent skeletal complications after bone metastasis; the relation between ZA treatment persistency and length of follow-up; the relation between ZA treatment persistency and monthly rate of skeletal complications; and the association between administering ZA at the recommended dosing schedule (every 3–4 weeks)¹³ versus other dosing schedules and no treatment with the development of skeletal complications.

Skeletal complications were defined as 1 of 4 events: radiation treatment, spinal cord compression, pathologic fractures, and surgery to the bone. According to the US label, the recommended dosing interval for ZA is every 3 to 4 weeks¹³ (to sustain the effect). Therefore, persistency was defined as treatment duration with the absence of a gap >45 days between 2 consecutive ZA treatments (every 3–4 weeks). The number of skeletal complications experienced after bone metastasis was standardized on a per-month basis. The length of follow-up was defined as the duration (months) from the date of bone metastasis diagnosis to the date of the last claim found for the patient in the dataset.

Risk characteristics for all comparison groups were identified, and comorbid conditions were used as a means of calculating each patient's Charlson Comorbidity Index (CCI). The CCI assesses a patient's overall severity of condition,^{14,15} which is computed based on type and weight given to each comorbid condition. The lower the CCI score, the less severe the patient's overall condition. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) codes were used to identify cancer type, bone metastases, and for skeletal complications (Table 1).

Statistical Analyses

Analysis of variance (ANOVA) tests and *t* tests were used to compare outcomes between groups. Multiple regression models were used to assess the association between ZA treatment and rates of skeletal complications controlling for age and CCI. Regression models also were used to assess the relation between ZA treatment and length of follow-up controlling for age and CCI. Cox regression models were used to investigate the relation between ZA treatment persistency and likelihood of continuing follow-up. The results presented were calculated for the combined cohort of all patients with breast, prostate, or lung cancer.

RESULTS

Of the 78,782 cancer patients in the PharMetrics dataset who had ≥ 1 bone metastasis diagnosis during the study period, 4546 patients met additional inclusion criteria: These included 1508 patients in the ZA-treated group and 3038 patients in the untreated group (Fig. 1).

Demographics

Overall, 46.1%, 34.2%, and 24.0% of patients with cancer of the breast (women), prostate, and lung, respectively, received ZA. Patients with prostate cancer were significantly older than patients with lung or breast cancer ($P < .05$). Patients with breast cancer had the lowest CCI, and patients with lung cancer had the highest CCI ($P < .05$). Significant differences were observed between the ZA-treated group and the untreated group for age, sex, and CCI ($P < .001$) (Table 2).

Monthly Follow-up Duration

Compared with no treatment, the mean follow-up ($\pm$ standard deviation) for patients who received ZA was 3 months longer (8.7 ± 9.28 vs 12.2 ± 9.05 months, respectively; $P < .001$).

Monthly Rates of Skeletal Complications

Compared with no treatment, ZA use was associated with a 33% reduction in the monthly rate of skeletal complications (0.43 ± 0.4 per month vs 0.29 ± 0.3 per month, respectively; $P < .001$).

Relation Between ZA Treatment Persistency and Clinical Outcome

Patients who persisted longer on the scheduled treatment without a gap had better outcomes; for example, those who persisted for >180 days had better outcomes than those who persisted for <180 days. Persistent use of ZA every 3 to 4 weeks was associated with a longer follow-up duration compared with less frequent dosing ($P < .05$) (Table 3) and, according to Cox regression modeling (which was controlled for CCI and age), a greater probability of continuing follow-up (Fig. 2). Greater persistency in ZA use also was associated with lower monthly rates of skeletal complications ($P < .05$) (Fig. 3). This benefit was demonstrated beyond 1 year of use.

Time From Bone Metastasis to First and Second Skeletal Complications (in Patients Without Previous Skeletal Complications)

Among the patients who did not have skeletal complications before ZA initiation (subgroup analysis), ZA treatment was associated with an almost 2-fold greater time to the first skeletal complication and a delayed time to the second skeletal complication compared with patients in the untreated group (who developed a skeletal complication after bone metastasis diagnosis) (Fig. 4). The mean time to first skeletal complication was 185 ± 210 days in the ZA-treated group versus 98 ± 161 days in the untreated group ($P < .0001$). The mean time from first to second skeletal complication was 111 ± 124 days in the ZA-treated group versus 86 ± 114 days in the untreated group ($P < .05$).

Relation Between ZA Dosing Schedule, Monthly Rates of Skeletal Complications, and Follow-up Duration

During the first 6 months of treatment, the use of ZA according to the recommended dosing schedule (every 3–4 weeks) was associated with a significantly longer length of follow-up (17.11 months) compared with the use of ZA at nonrecommended dosing schedules (9.93 months) and no treatment (8.68 months; ANOVA test; $P < .001$). Similarly, patients who received ZA at the recommended dosage schedule (every 3–4 weeks) experienced a lower rate

of skeletal complications (0.16 events per month) compared with patients who did not follow the recommended dosing schedule (0.31 events per month) and untreated patients (0.43 events per month) (Fig. 5). One-year data (albeit with a smaller number of ZA users [$n = 605$] and nonusers [$n = 1436$]) demonstrated a similar pattern for both parameters. The use of ZA according to the recommended dosing schedule (every 3–4 weeks) was associated with significantly longer length of follow-up (21.5 months) compared with the use of ZA at nonrecommended dosing schedules (17.6 months) and no treatment (15.9 months; ANOVA test; $P < .001$). Similarly, patients who received ZA at the recommended dosage schedule (every 3–4 weeks) experienced a lower rate of skeletal complications (0.12 events per month) compared with patients who did not follow the recommended ZA dosage schedule (0.15 events per month) and patients in the untreated group (0.17 events per month; ANOVA test; $P < .001$).

DISCUSSION

Skeletal complications from bone metastasis result in substantial morbidity, including debilitating pain, pathologic fracture, and spinal cord or nerve root compression.^{1,2} Bisphosphonates play an important role in reducing skeletal morbidity and are an integral part of the overall management strategy for malignant bone disease.^{2,9}

ZA is the only bisphosphonate to date that has broad efficacy in the treatment of bone metastases from all solid tumor types, including lung and prostate cancers.⁸ To our knowledge, this study is the first to investigate the impact of ZA treatment in the real-world, clinical practice environment. By using a claims database, we sought to identify patterns of ZA prescribing in clinical practice and evaluated the associated clinical outcomes. The skeletal complications evaluated in our study were consistent with those defined as endpoints in ZA clinical trials.^{10–12}

The strength of the apparent relation between ZA use and clinical outcomes observed in our retrospective analysis corroborated data obtained in ZA clinical trials. In both settings, ZA use was associated with a significantly reduced risk of developing a skeletal complication and a longer time between events compared with placebo.

Clinical trials have reported lower rates of skeletal events (excluding hypercalcemia of malignancy) in patients who received ZA compared with those who received placebo. Among patients with breast cancer, ZA use reduced the percentage of patients with at least 1 skeletal event to 29.8% for patients who received ZA 4 mg versus 49.6% for patients who received placebo ($P = .003$).¹¹ In a trial of patients with nonsmall cell lung cancer or other tumor types (excluding breast or prostate cancers),¹⁰ the skeletal morbidity rate (defined as the number of skeletal events per year) was 2.24 ± 9.12 events per year for patients who received ZA 4 mg versus 2.52 ± 5.11 events per year for patients who received placebo ($P = .069$). In a trial of patients with prostate cancer, the skeletal morbidity rate (defined as the number of skeletal events divided by the time at risk in years) was 0.8 (95% confidence interval [CI], 0.57–1.03) in patients who received ZA 4 mg versus 1.49 (95% CI, 1.03–1.94) for patients who received placebo ($P = .006$).¹² Similarly in our retrospective analysis, ZA use was associated with a 33% reduction in the monthly rate of skeletal complications compared with no treatment. The follow-up for patients receiving ZA was 3 months longer compared with the follow-up for patients in the untreated group.

ZA treatment significantly prolonged the time to onset of first skeletal event, both in the clinical trial setting and in the real-world treatment setting. For example, in the clinical trial of patients with nonsmall cell lung cancer and other solid tumors (excluding breast or prostate), the median time to first skeletal event (excluding hypercalcemia of malignancy) was 230 days for patients who received ZA 4 mg versus 163 days for patients who received placebo ($P = .023$).¹⁰

Similarly, in a study of patients with bone metastases from prostate cancer,¹² the time to first occurrence of skeletal-related event was ≥ 420 days in the ZA 4-mg treatment group versus a median of 321 days in the placebo group ($P = .011$). In our retrospective analysis, the subgroup of patients without skeletal complications before the initiation of ZA had an almost doubled time to the first skeletal complication and had a delayed time to the second skeletal complication relative to no treatment.

Our study revealed that greater persistency with ZA was associated with a longer length of follow-up and a lower monthly rate of skeletal complications compared with no treatment. For both of these persistency endpoints, the beneficial association was sustained beyond 1 year of ZA use. We also observed that, during the first 6 months of therapy, use of ZA at the recommended dosing schedule (every 3–4 weeks) was associated with a reduction $\geq 48\%$ in the monthly rate of skeletal complications compared with the less frequent administration schedule or no treatment.

In this retrospective analysis, the rate of ZA use before development of skeletal complications was low. Between January 2002 and October 2005, 27% of patients with bone metastases in the ZA-treated group received ZA before the first skeletal complication. Our findings suggest an apparent benefit of starting ZA at the time bone metastases are diagnosed. This observation, however, may reflect clinical practice only in part, because our study included only patients with a history of at least 1 skeletal complication. It is possible that ZA was prescribed prophylactically for some patients in the PharMetrics dataset; however, if they never developed a skeletal complication during the study period, then they were excluded from the analysis.

For this study, we used the *first date of bone metastasis* as the index date for the computation of outcomes (skeletal morbidity rate and length of follow-up) for both the treated and untreated groups. (The *time since ZA initiation* could not serve as the index date, because there was no comparable time frame for the nontreated patients). Because most of patients who were included in our study had experienced their first skeletal complication before they were started on ZA, the monthly rates of skeletal complications were greater than those reported in clinical trials in which comparable baselines were ensured by treating the time of randomization to treatment versus no treatment as the ‘index date.’ Thus, our approach was conservative in nature; using the *time since bone metastasis* rather than the *time since ZA initiation* most likely biased the results against ZA rather than in favor of ZA.

The somewhat lower than anticipated use of ZA in this study cohort (46.1%, 34.2%, and 24% of patients with breast, prostate, and lung cancer, respectively) may have been a reflection of several issues, including the finding that these claims data lagged at least 1 year behind actual usage data. The rate of adoption of ZA increased with time after its market introduction in the United States. The current study time frame was only 3 years since the introduction of ZA to the market. Moreover, because inclusion criteria stipulated a diagnosis of bone metastasis and experience of at least 1 skeletal complication, patients who were treated with ZA who never experienced skeletal complications were not included in the study. In addition, the decision not to give ZA may be based on numerous factors, including the extent of nonskeletal disease. This parameter may have been captured in part by the CCI, which assesses a patient’s overall severity of condition.

Our ability to identify skeletal complications and potential drug-related adverse effects depended on the availability of unique identifiers, such as ICD-9 or Common Procedural Terminology (CPT) codes, which did not capture related conditions or adverse events. This drawback is discussed in the below (see Limitations). Because bone metastasis and skeletal complications were part of the inclusion criteria, we did not address the preventative role of ZA in the development of bone metastases.

Limitations

Our study had the inherent limitations associated with a retrospective analysis using a claims database. An effort was made to delineate the relation between outcomes based on ZA treatment regimen; however, the temporal relation hinged on when the provider submitted a claim relevant to the study endpoint. The date of drug administration was based on the date of the claim, which may or may not have coincided with the actual prescription or administration date.

Lack of ZA persistency (eg, the use of ZA less frequently than recommended) may have reflected customization of the ZA treatment regimen for patients with a poor performance status who had troublesome nonskeletal disease at other sites. Such a practice could have biased the study results. Given the nature of a claims dataset design, data on performance status were not available for this study cohort.

Calculating the length of follow-up was based on the date of last claim, which may indicate that a patient has died, discontinued using health services (potentially as a result of tolerability issues), or disenrolled from a health plan. Because of the claims dataset study design, our ability to capture information on skeletal complications and potential drug-related adverse effects depended on the availability of unique identifiers, such as ICD-9 or CPT codes. To address conditions/issues that are not captured with these unique identifiers would require a study design based on actual chart review. This limitation must be balanced with the ability of a claims database design like that used in the current work to evaluate patient outcomes based on a larger sample than can be studied in a chart review-based study.

Other limitations were that the uneven breakdown of patients by cancer type and the associated physician treatment patterns may have affected the results; the PharMetrics database was employer based, potentially limiting the number of patients with prostate cancer (which often afflicts the elderly population). In addition, the study results were based on combined analyses of patients with solid tumors of the breast, prostate, or lung, and small sample sizes prevented the analysis of results by cancer type.

In addition, although the CCI adjusted for the comorbidity of the study cohort (proxy for overall severity of condition), the severity of cancer, bone involvement, and extent of nonskeletal disease may not have been captured completely by this index, which may have biased the study results. The extent of nonskeletal disease may have been an underlying factor in the relatively low percentage of ZA use in this study.

Finally, the findings from the current study pertain specifically to patients who have experienced skeletal complications based on inclusion criteria. Therefore, these results cannot be extrapolated to patients who receive ZA and never experience skeletal complications. Further evaluation of the benefits of ZA for the latter patient population is warranted.

In conclusion, although it is not possible to compare clinical trials data directly with claims data analyses, both ZA clinical trial data and real-world data indicate that ZA reduces the skeletal morbidity rate and delays the time to skeletal complications in patients with breast cancer (women), prostate cancer, or lung cancer. The current study provides evidence to the practicing oncology community of the impact of ZA use and prescribing patterns on clinical outcomes, thus helping practitioners make informed clinical decisions regarding treatment approaches for patients with bone metastases.

Acknowledgments

This study was supported by Novartis Pharmaceuticals.

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FIGURE 1.

Patient disposition. An asterisk indicates that patients in this group met 1 of several prespecified chronologic events; a dagger indicates that patients met 1 of the following 3 chronologic events: bone metastases→zoledronic acid (ZA) use→skeletal complication (ZA-treated group); the same date for bone metastasis and ZA use→skeletal complication (ZA-treated group); bone metastases→skeletal complication, no ZA use (untreated group).

FIGURE 2.
Zoledronic acid persistency was associated with greater probability of continuing follow-up.

FIGURE 3.

Treatment persistency was associated with a lower monthly rate of skeletal complications. Persistence was defined as the absence of a gap >45 days between ZA administrations. A regression model that controlled for age and Charlson Comorbidity Index was used to assess the relation between ZA treatment and rates of skeletal complications.

FIGURE 4.

The use of zoledronic acid (ZA) was associated with a doubled time to first skeletal complication ($P < .0001$; t test) and a delayed time to second skeletal complication ($P < .05$; t test) compared with untreated patients.

FIGURE 5.

The use of zoledronic acid (ZA) at the recommended dosage schedule (every 3–4 weeks) was associated with a reduced rate of skeletal complications (analysis of variance, $P < .001$; post hoc test with mean differences significant for all paired comparisons; $P < .05$).

TABLE 1

Codes from the International Classification of Diseases, 9th Revision, Clinical Modification

Cancer Type	ICD-9 CM Code(s)
Lung cancer	162.XX, 162, 162.0, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9
Breast cancer (women)	174.XX, 174, 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9
Prostate cancer	185
Bone metastasis	
Secondary malignant neoplasm of bone and bone marrow	198.5
Skeletal complication	
Radiation treatment delivery	eg, 77413 (CPT-4 Code)
Spinal cord compression	eg, 336.9
Pathologic fracture	eg, 733.13
Surgery to the bone	eg, 78.10

ICD-9 CM indicates International Classification of Diseases, 9th Revision, Clinical Modification; CPT-4, Common Procedural Terminology, 4th edition.

TABLE 2

Baseline Characteristics

Characteristic	Zoledronic Acid Treated Group (n = 1508)	Untreated Group (n = 3038)	P
Charlson Comorbidity Index, mean $\pm$ SD	8.59 $\pm$ 0.9	8.93 $\pm$ 1.3	<.001 [*]
Age, mean $\pm$ SD y	55.10 $\pm$ 9.4	58.22 $\pm$ 2.4	<.001 [*]
Women/men, %	65.2/34.8	52.8/47.2	<.001 [†]

SD indicates standard deviation.

^{*} *T* test.

[†] Pearson chi-square test.

TABLE 3

Persistent Use of Zoledronic Acid Was Associated With Longer Follow-up Duration *

Treatment Persistency, d*	Follow-Up Duration, mo
Untreated	8.7
31–90	9.6
91–180	11.5
181–365	14.8
>365	22.6

* Treatment persistency was defined as the absence of a gap >45 days between zoledronic acid treatments.