Risk of Jaw Osteonecrosis After Intravenous Bisphosphonates in Cancer Patients and Patients Without Cancer

James S. Goodwin, MD; Jie Zhou, PhD; Yong-Fang Kuo, PhD; and Jacques Baillargeon, PhD

Abstract

Objective: To compare the risk of jaw osteonecrosis after intravenous (IV) bisphosphonate administered to patients with cancer vs patients without cancer.

Patients and Methods: We conducted a retrospective cohort study of a 5% national sample of Medicare patients administered IV bisphosphonate from January 1, 2008, through December 31, 2013, for cancer vs noncancer indications. Probable jaw osteonecrosis was estimated with an algorithm including diagnoses, surgical procedures, and imaging studies. A non-IV bisphosphonate comparison group included patients prescribed an oral bisphosphonate for 30 days or less.

Results: During follow-up, 40 (0.42%) out of 9482 patients with cancer developed probable jaw osteonecrosis compared with 8 (0.05%) out of 16,046 patients without cancer. In a Cox multivariable survival analysis controlling for patient characteristics and number of IV zoledronic infusions, patients without cancer had a hazard ratio of 0.17 (95% CI, 0.06-0.46) for developing jaw osteonecrosis compared with those with cancer. The lower rate of jaw osteonecrosis in patients without cancer was also confirmed in a number of sensitivity analyses.

Conclusion: The low rate of jaw osteonecrosis in patients with osteoporosis who receive IV bisphosphate should be weighed against the benefit of those agents in preventing hip and other fractures.
rate has been ascribed to the lower doses received by patients with osteoporosis compared with patients with cancer. Patients with cancer frequently received 20 or more doses, particularly before the recognition of jaw osteonecrosis as a toxicity. In addition, other treatments received by patients with cancer might interact with bisphosphonates in promoting jaw osteonecrosis. However, there have been no head-to-head dose comparisons of jaw osteonecrosis after IV bisphosphonates for cancer vs non-cancer indications. In this report, we compare the incidence of jaw osteonecrosis among patients with cancer versus patients without cancer who received IV bisphosphonates. In particular, we were interested in the incidence rates among patients who received a low number of total infusions, which would be the usual case in a patient with osteoporosis. After controlling for dose, are there still differences in the risk of jaw osteonecrosis between patients with and without cancer? We used Medicare data from 2008 to 2013 to identify patients with and without cancer receiving IV bisphosphonates and to follow them for evidence of the development of jaw osteonecrosis. As a comparison, we included patients without cancer for whom an oral bisphosphonate was prescribed but who took it only for a month or less.

The limitations of claims-based algorithms do not allow for precision in estimating the absolute incidence of jaw osteonecrosis. However, we reasoned that such algorithms should still allow us to estimate differences in rates of jaw osteonecrosis experienced by patients with and without cancer after exposure to similar doses of IV bisphosphonate.

**METHODS**

**Cohorts**

The main cohort included any patient aged 65 years or older who had received an infusion of an IV bisphosphonate in the period 2008 to 2013, and had Medicare Part A and B coverage with no health maintenance organization enrollment in the 12 months before the initial infusion. We used the Health Care Procedure Coding System drug administration code J2430 for pamidronate; J3487, J3488, and J3489 for zoledronic acid; J1436 for etidronate disodium; and J1740 for ibandronate sodium. We excluded patients who had any diagnosis of head and neck cancer (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 140.x to 149.x) because radiotherapy for such cancers can damage jaw and facial bones. We also excluded those who received denosumab in the 12 months before the initial IV bisphosphonate infusion. Denosumab is a monoclonal antibody used for osteoporosis that has also been associated with jaw osteonecrosis. The cohort was stratified into those with a cancer listed as the first or second diagnosis in the Medicare claim for the bisphosphonate infusion, vs all others. From the patients who did not have a cancer diagnosis as the first or second diagnosis on a claim for an IV bisphosphonate, we excluded any who had a cancer diagnosis associated with any Medicare claim in the year before their first IV bisphosphonate infusion. This left us with 11,098 patients with cancer and 18,361 patients without cancer who received at least 1 dose of IV bisphosphonate. In the cancer cohort, 90% had a cancer diagnosis in the first position on a claim for IV bisphosphonate. For the 10% with a cancer diagnosis in the second position, the most common diagnoses in the first position were related to chemotherapy administration.

As a comparison, we also constructed a cohort from Medicare Part D files of patients aged 65 years or older who were given prescriptions with a total drug supply of 30 days or less for an oral bisphosphonate from January 1, 2008, through December 31, 2013. We reasoned that these patients would resemble the patients who received IV bisphosphonates, but because of the 1 month or less supply of oral bisphosphonate, they could be considered as untreated. We deleted patients who had received either IV bisphosphonate or denosumab or those with a diagnosis of cancer in the previous 12 months, leaving a cohort of 6880. The University of Texas Medical Branch provided Institutional Review Board approval to conduct the study.

**Patient Characteristics**

Beneficiary age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), and Medicaid eligibility were extracted...
from the Medicare Denominator Files. Elixhauser comorbidities were identified by reviewing all diagnoses associated with all claims for the previous 12 months.22

**Definition of Outcomes**

Our approach to defining osteonecrosis of the jaw was similar to our earlier studies.15,16 In exploratory analyses, we examined the detailed trajectories in the Medicare records of provider visits, procedures, tests, and diagnoses in patients who had received IV bisphosphonate. In particular, we studied the trajectories of patients with either a diagnosis of jaw osteonecrosis or inflammatory conditions of the jaw, or who had a procedure such as surgery or imaging studies of the jaw or facial bones (for list, see Supplemental Table, available online at http://www.mayoclinicproceedings.org). We then reviewed all claims in the 6 months before and 12 months after the initial diagnosis or procedure to look for patterns.

This approach led us to define probable osteonecrosis of the jaw as any patient who had a claim with a diagnosis of jaw osteonecrosis (ICD-9-CM code 733.45) on at least 2 occasions, and who had a surgical or imaging procedure on either the jaw or facial bones before at least 1 of the diagnoses of osteonecrosis of the jaw.

| TABLE 1. Baseline Characteristics for the Patients Given Intravenous Bisphosphonate for a Cancer Indication vs for a Noncancer Indication, as Well as Patients Receiving Oral Bisphosphonates for a Month or Less |
|---------------------------------|---------------------------------|---------------------------------|
| Patient characteristics        | Cancer (N=11,098)               | Noncancer (N=18,361)            |
| Comorbidity, n (%)              | 0                               | 1                               |
|                                | 5462 (49.22)                    | 9799 (53.37)                    |
|                                | 1                               | 2895 (26.09)                    |
|                                | 1434 (12.92)                    | 2025 (11.03)                    |
|                                | 1307 (11.78)                    | 1474 (8.03)                     |
| Medicaid eligible              | No                              | Yes                             |
|                                | 9987 (89.99)                    | 1111 (10.01)                    |
|                                | 16,329 (88.93)                  | 2032 (11.07)                    |
|                                | 4649 (67.57)                    | 2231 (32.43)                    |
| Age (y)                        | ≤65-69                          | ≤70-74                          |
|                                | 2238 (20.17)                    | 2816 (25.37)                    |
|                                | 2646 (23.84)                    | 1994 (17.97)                    |
|                                | 1404 (12.65)                    | 1111 (10.01)                    |
|                                | 3165 (17.24)                    | 4102 (22.34)                    |
|                                | 4346 (23.67)                    | 3803 (20.71)                    |
|                                | 2945 (16.04)                    | 1273 (18.50)                    |
| Race/ethnicity                 | White                           | Black                           |
|                                | 9583 (86.35)                    | 845 (7.61)                      |
|                                | 16695 (90.93)                   | 427 (3.85)                      |
|                                | 5326 (77.41)                    | 243 (2.19)                      |
|                                | 547 (2.98)                      | 476 (2.59)                      |
|                                | 461 (6.70)                      | 348 (5.06)                      |
| Sex                            | Male                            | Female                          |
|                                | 4915 (44.29)                    | 6183 (55.71)                    |
|                                | 1021 (5.56)                     | 17,340 (94.44)                  |
|                                | 584 (8.49)                      | 6296 (91.51)                    |
| Type of drug                   | Etidronate                      | Ibandronate                     |
|                                | 1 (0.01)                        | 93 (0.84)                       |
|                                | 3 (0.02)                        | 1623 (8.84)                     |
|                                | 3 (0.02)                        | 155 (0.84)                      |
|                                | 493 (4.44)                      | 534 (2.91)                      |
| Number of infusions            | 1-2                             | 3-4                             |
|                                | 3709 (33.42)                    | 1863 (16.79)                    |
|                                | 12,304 (67.01)                  | 4339 (23.63)                    |
|                                | 853 (4.65)                      | 865 (4.71)                      |
|                                | 3709 (33.42)                    | 1863 (16.79)                    |
|                                | 12,304 (67.01)                  | 4339 (23.63)                    |
|                                | 853 (4.65)                      | 865 (4.71)                      |
|                                | 3709 (33.42)                    | 1863 (16.79)                    |
|                                | 12,304 (67.01)                  | 4339 (23.63)                    |
|                                | 853 (4.65)                      | 865 (4.71)                      |
Statistical Analyses

Descriptive analysis was used to summarize the patient characteristics. We used the Kaplan-Meier method to estimate unadjusted event-free survival and Cox proportional hazards regression for time to the first occurrence of the outcome. The log-rank test was used to select the significant variables to be included in the Cox proportional hazards model. A P value of less than .05 was considered significant. Martingale residuals was used to test the proportional hazard assumption in the Cox model, and the results satisfied the assumption.23

Patients were entered into the analysis on the date of receipt of their first IV bisphosphonate infusion, and censored at a death, at a denosumab prescription, at loss of Medicare Part A or Part B coverage, enrollment in a health maintenance organization, or at the end of study (December 31, 2013). The main analyses were restricted to patients who received only zoledronic acid.

In sensitivity analysis, we broadened the outcome by including all patients who were given at least 1 diagnosis of osteonecrosis of the jaw (ICD-9-CM code 733.45) whether or not surgery or imaging studies of the jaw or facial bones were performed. We also included ICD-9-CM code 526.4 for “inflammatory conditions of the jaw” in the algorithm for identifying patients with jaw osteonecrosis. In other analyses, we broadened the study cohort to include all patients who had received any IV bisphosphonate, not just those who received zoledronic acid. All analyses were performed using SAS 9.4 (SAS Institute).

RESULTS

The final cohort of patients receiving IV bisphosphonates numbered 29,459. Of these, 11,098 had a cancer as the first or second diagnosis for a bisphosphonate claim. Approximately 46% of these were breast cancer, 22% genitourinary cancer, 14% lung cancer, 12% multiple myeloma, and 6% gastrointestinal cancer. The remaining 18,361 patients did not have a cancer diagnosis on either the claims for IV bisphosphonate or any claim in the 12 months before the first IV bisphosphonate infusion. The primary diagnoses listed on the claims for these patients included osteoporosis/osteopenia (90%), Paget disease (1%), disorder of calcium metabolism (0.4%), and other diagnoses (8.6%). The characteristics of the patients with and without cancer who received IV bisphosphonate are presented in Table 1. Also shown is the cohort of patients without cancer who received a 30-day supply or less of an oral bisphosphonate. The 2 cohorts without cancer were overwhelmingly female, while the cohort with cancer was more evenly balanced. The cohorts without cancer were also somewhat older.

Most (>85%) of the patients in each IV bisphosphonate cohort received zoledronic acid. The distribution of total doses differed by cohort, with 50% of patients with cancer receiving 5 or more doses vs fewer than 10% of patients without cancer. Because the different types of IV bisphosphonate differ in strength and recommended frequency of administration, we restricted our main analyses to the 25,528 patients who received only zoledronic acid, although we included all patients in some of the sensitivity analyses discussed later.

Among the 25,528 patients who received only IV zoledronic acid, there were 48 cases of probable jaw osteonecrosis over a maximum
of 6 years of follow-up: 40 (0.42%) among the cohort with cancer (N=9,482) and 8 (0.05%) among the cohort without cancer (N=16,046). The Kaplan-Meier curves representing the probability of patients not having jaw osteonecrosis since the first infusion during follow-up are presented in the Figure. Only those patients who received 1 to 5 infusions of zoledronic acid are included (n=5,548 patients with cancer and 15,998 patients without cancer). The 6-year probability of developing jaw osteonecrosis was 0.61 (95% CI, 0.31%-1.23%) for patients with cancer receiving IV zoledronic acid. The 6-year probability of developing jaw osteonecrosis was 0.08% (95% CI, 0.04%-0.18%) for patients without cancer receiving IV zoledronic acid. The probabilities for patients with cancer vs patients without cancer were significantly different by log-rank test (P<.001). Also shown are the patients who received 30 days or less of an oral bisphosphonate, with a jaw osteonecrosis rate of 0%.

To further explore the lower rate of jaw osteonecrosis in patients without cancer vs patients with cancer, we combined the 2 cohorts of patients with cancer and patients without cancer who had received zoledronic acid in a Cox multivariable survival analysis of risk of jaw osteonecrosis. In preliminary analyses, only patient sex was significantly associated with jaw osteonecrosis by log-rank test (P<.001). This was included in the Cox model, along with the number of zoledronic acid infusions, and whether the patient had cancer. In these analyses, we removed patients who had 6 or more infusions because the cohort without cancer had few such cases. As shown in Table 2, there are no significant associations between the hazard of jaw osteonecrosis and the number of zoledronic acid infusions (1-5) and sex. The CIs for these estimates are broad because of the limited number of patients with the outcome (n=19). (There was a dose-response relationship for zoledronic acid and hazard of jaw osteonecrosis in patients with cancer, but this started at a higher number of doses than was included in Table 2.) There was a clear and highly significant association between the indication for the IV bisphosphonate infusion and the hazard of jaw osteonecrosis, even after controlling for the total number of infusions. Those with noncancer indications were only one-sixth as likely to develop osteonecrosis of the jaw (hazard ratio, 0.17; 0.06-0.46).

In sensitivity analyses, we included patients who had received any IV bisphosphonate (zoledronic acid, pamidronate, ibandronate, or etidronate) in analyses similar to those shown in Table 2. The hazard of jaw osteonecrosis for patients without cancer remained low compared with that for patients with cancer (hazard ratio, 0.14; 0.05-0.37).

We also conducted sensitivity analyses in which we broadened the criteria for the outcome of jaw osteonecrosis. Although this increased the estimated risk of jaw osteonecrosis, it did not affect the large difference in the rates of the outcome between patients with and without cancer. For example, when the outcome of jaw osteonecrosis was broadened to include any patient with at least 1 diagnosis of jaw osteonecrosis (ICD-9-CM code 733.45), whether or not a procedure or imaging study was performed, the hazard of jaw osteonecrosis in patients without cancer was 0.22 (95% CI, 0.12-0.42), compared with patients with cancer.

<p>| TABLE 2. Multivariable Survival Analysis of Hazard of Developing Jaw Osteonecrosis as a Function of the Indication for the Intravenous Bisphosphonate Infusion, Controlling for Other Characteristics, for Patients Who Received 5 or Fewer Infusions of Zoledronic Acid |
|---------------------------------|------------------|-----------------|</p>
<table>
<thead>
<tr>
<th><strong>Patient characteristics</strong></th>
<th><strong>Number of patients (total 21,546)</strong></th>
<th><strong>Hazard (95% CI) for jaw osteonecrosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infusions</td>
<td>1.10 (0.79-1.53)</td>
<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3197 (14.84)</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>18,349 (85.16)</td>
<td>0.41 (0.14-1.17)</td>
</tr>
<tr>
<td>Indication for bisphosphonate, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>5548 (25.75)</td>
<td>Reference</td>
</tr>
<tr>
<td>Noncancer</td>
<td>15,998 (74.25)</td>
<td>0.17 (0.06-0.46)</td>
</tr>
</tbody>
</table>
DISCUSSION

There is little doubt that IV bisphosphonates can cause osteonecrosis of the jaw. This condition was exceedingly rare until the 1990s, when it became increasingly more common and almost entirely limited to patients with cancer who had received IV bisphosphonates either to treat or to prevent bone metastasis.\(^\text{14,15}\) The question posed by our analyses was whether patients who receive IV bisphosphonates for indications other than cancer experience a similar risk of jaw osteonecrosis. The results suggest that the risk is considerably lower, even after controlling for the number of IV bisphosphonate infusions.

Information on rare and/or late toxicities is difficult to obtain. Clinical trials rarely include sufficient numbers of patients, and their follow-up is often not long enough to assess late toxicities. Administrative data have the advantage of large numbers of exposed patients, generally with longer follow-up time than in clinical trials, but the algorithms to identify toxicities have important limitations. Previous attempts to identify cases of osteonecrosis of the jaw using claims data have been hindered by the lack of a specific ICD-9-CM code for this condition.\(^\text{24-29}\) The ICD-9-CM code 733.45, “osteonecrosis of the jaw,” was introduced only in 2007. Before that, a code for “inflammatory conditions of the jaw” was often used. This and other diagnosis codes potentially related to jaw osteonecrosis have low positive predictive values for jaw osteonecrosis when used by themselves.\(^\text{24-29}\) In our preliminary analyses, we found that the specific ICD-9-CM code for osteonecrosis of the jaw was sometimes used in a “rule out” manner: for example, when a provider ordered one of the collagen cross-links blood tests to assess the risk of jaw osteonecrosis.\(^\text{30,31}\)

Our approach was to combine diagnosis codes with a surgery procedure or imaging study of the facial or jaw bones. It is important to recognize that this method for identifying cases of jaw osteonecrosis with Medicare claims has not been validated. We will not argue for its complete accuracy. Rather, we reason that any limitation of those algorithms would not be responsible for the difference in risk between patients with and without cancer, which was the main purpose for the study. We could not come up with a plausible mechanism whereby the sensitivity and specificity of the algorithm would differ between patients with and without cancer to an extent that could result in a 6-fold difference in the hazard of jaw osteonecrosis. By 2008 to 2013, the period of our study, jaw osteonecrosis had achieved widespread notoriety in the medical and lay press,\(^\text{11-14}\) reducing the likelihood of substantial numbers of undiagnosed cases.

As a comparison group, we included patients who had received a 30-day or less supply for an oral bisphosphonate prescription. We reasoned that these patients would be the most appropriate “nontreatment” group with which to compare patients given IV bisphosphonate, in that the indications would be similar but the exposure to bisphosphonates very different. None of these patients developed probable jaw osteonecrosis by our algorithm.

Our study has a number of limitations. We have already discussed the limitations of the algorithm used to identify jaw osteonecrosis. Other limitations include the exclusion of patients younger than 65 years and those in Medicare managed care programs. Also, we did not estimate the incidence of other late toxicities of IV bisphosphonates. In addition to jaw osteonecrosis, late toxicities include atypical subtrochanteric fractures.\(^\text{10}\) These have not been reported in the randomized trials, but meta-analyses of case-control and cohort studies suggest that the rate is lower than that reported for jaw osteonecrosis.\(^\text{3,10}\)

A number of national organizations and authorities have recently decried the low treatment rates for osteoporosis, even in high-risk patients with previous fractures.\(^\text{1,3,9}\) A case could be made that IV bisphosphonates are underused in patients with osteoporosis. As noted by several authors, the risk of hip fracture in untreated patients with osteoporosis is much greater than the risk of jaw osteonecrosis.\(^\text{1,3}\) In a randomized controlled trial of zoledronic acid after hip fracture, Lyles et al.\(^\text{18}\) reported a 4.3% absolute risk reduction of any
subsequent fracture over a median follow-up of 1.9 years. Another randomized trial of zoledronic acid in 7230 women with osteoporosis found a significant absolute reduction of 7.6% in vertebral fractures and 0.9% in hip fractures at 3 years. Absolute risk reductions increase with age and with length of follow-up. These reductions compare to an absolute increase of 0.08% in the risk of jaw osteonecrosis over 6 years found in our study, and to the estimates of 0% to 0.04% reported in a 2014 update from the American Association of Oral and Maxillofacial Surgeons.

CONCLUSION
There is growing concern about the preventable morbidity and mortality associated with untreated osteoporosis, especially in high-risk patients such as those with previous fractures. Fear of jaw osteonecrosis is thought to be an important driver of that undertreatment. Our data, combined with the results of previous studies, suggest that the risk of jaw osteonecrosis after IV bisphosphonate is considerably lower in patients with osteoporosis than in patients with cancer.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification; IV = intravenous


REFERENCES