Published in final edited form as:

Mayo Clin Proc. 2017 January ; 92(1): 106–113. doi:10.1016/j.mayocp.2016.09.015.

Risk of jaw osteonecrosis after intravenous bisphosphonates in cancer patients and patients without cancer

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Abstract

Objective—To compare the risk of jaw osteonecrosis after intravenous (IV) bisphosphonate administered to patients with cancer versus to non-cancer patients.

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. non cancer 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 9,482 cancer patients developed probable jaw osteonecrosis compared to 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% Confidence Interval: 0.06 - 0.46) for developing jaw osteonecrosis compared to those with cancer. The lower rate of jaw osteonecrosis in non-cancer patients was also confirmed in a number of sensitivity analyses.

Conclusions—The low rate of jaw osteonecrosis in patients with osteoporosis who receive IV bisphosphonate should be weighed against the benefit of those agents in preventing hip and other fractures.

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Conflict of interest disclosure: None of the authors have any conflicts of interest to disclose.

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Introduction

Osteoporosis is a common and morbid condition, responsible for an estimated 1.5 million fractures yearly in the US.¹⁻³ Several classes of drugs are approved for the prevention or treatment of osteoporosis.⁴ Of these, bisphosphonates are the most widely used. Oral bisphosphonates have been shown to reduce both vertebral and non-vertebral fractures in large randomized controlled trials.⁴ The effectiveness of oral bisphosphonates can be reduced because of high rates of non-adherence as well as variable absorption of the drug.^{2, 4}

Intravenous (IV) bisphosphonates have also been approved for osteoporosis treatment. IV administration avoids the absorption issues that limit the effectiveness of oral bisphosphonates. Once yearly IV zoledronic acid reduced vertebral fractures by 70% and hip fractures by 41% in a randomized trial in women with low bone mineral density.⁵ However, use of both IV and oral bisphosphonate for osteoporosis has declined substantially in the last decade,⁶⁻⁸ driven by concerns about toxicity.^{1, 3, 6, 8-10} Among the toxicities, osteonecrosis of the jaw has garnered the most attention in the lay press.¹¹⁻¹³ Jaw osteonecrosis was noted in an escalating series of case reports in cancer patients who received IV bisphosphonate to prevent or treat bone metastases.¹⁴ Jaw osteonecrosis varies in severity, ranging from mild cases that can be treated with antibiotics to cases requiring debridement, resection and eventual reconstruction¹⁴.

The risk of jaw osteonecrosis after IV bisphosphonate in cancer patients is dose dependent, and was estimated at 1% to 5% over five years.¹⁵ The rate of jaw osteonecrosis after IV bisphosphonate given for osteoporosis is thought to be lower, based on the number of case reports and its absence in the randomized trials.^{4, 14, 16-20} This lower rate has been ascribed to the lower doses received by osteoporosis patients compared to cancer patients. Cancer patients frequently received 20 or more doses,^{14,15} particularly before the recognition of jaw osteonecrosis as a toxicity. In addition, other treatments received by cancer patients might interact with bisphosphonates in promoting jaw osteonecrosis.^{14, 15}

However, there have been no head-to-head dose comparisons of jaw osteonecrosis after IV bisphosphonates for cancer versus for non-cancer indications. In this report, we compare the incidence of jaw osteonecrosis among cancer versus non-cancer patients 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 risk of jaw osteonecrosis between cancer and non-cancer patients? We used Medicare data from 2008 to 2013 to identify cancer and non-cancer patients receiving IV bisphosphonates and to follow them for evidence of the development of jaw osteonecrosis. As a comparison, we included non-cancer patients for whom an oral bisphosphonate was prescribed but who only took it 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 cancer and non-cancer patients after exposure to similar doses of IV bisphosphonate.

Methods

Cohorts

The main cohort included any patient aged ≥ 65 who had received an infusion of an IV bisphosphonate in 2008-2013, and had Medicare Part A and B coverage with no health maintenance organization (HMO) enrollment in the 12 months before the initial infusion. We used the Health Care Procedure Coding System drug administration codes 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 prior to the initial IV bisphosphonate infusion. Denosumab is a monoclonal antibody used for osteoporosis that has also been associated with jaw osteonecrosis.²¹ The cohort was stratified into those with a cancer listed as the first or second diagnosis in the Medicare claim for the bisphosphonate infusion, versus 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 prior to their first IV bisphosphonate infusion. This left us with 11,098 cancer patients and 18,361 non-cancer patients who received at least one 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 who were given prescriptions with a total drug supply of ≤ 30 days 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 one 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 prior 12 months, leaving a cohort of 6,880. 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 prior 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 (see Supplemental Table for list). We then reviewed all claims in the six months prior and 12 months after the initial diagnosis or procedure to look for patterns.

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

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 $< .05$ 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 an HMO, or at the end of study (December 31, 2013). The main analyses were restricted to patients who only received zoledronic acid.

In sensitivity analysis, we broadened the outcome by including all patients who were given at least one diagnosis of osteonecrosis of the jaw (ICD-9-CM 733.45) whether or not surgery or imaging studies of the jaw or facial bones were performed. We also included ICD-9-CM 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, Cary, NC).

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% GI 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's disease (1%), disorder of calcium metabolism (0.4%) and other diagnoses (8.6%). The characteristics of the patients who received IV bisphosphonate with cancer and those without are given 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 two non-cancer cohorts were overwhelmingly female, while the cancer cohort was more evenly balanced. The non-cancer cohorts 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 cancer patients receiving five or more doses versus fewer than 10% of non-cancer patients. 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 six years of follow up: 40 (0.42%) among the cancer cohort (N=9,482) and 8 (0.05%) among the non-cancer cohort (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 Figure 1. Only patients who received 1-5 infusions of zoledronic acid are included (n= 5,548 cancer patients and 15,998 non-cancer patients). The six year probability of developing jaw osteonecrosis was 0.61 (95% Confidence Interval [CI] 0.31-1.23%) for patients with cancer receiving IV zoledronic acid. The six year probability of developing jaw osteonecrosis was 0.08% (95% CI: 0.04% - 0.18%) for non-cancer patients receiving IV zoledronic acid. The probability for the cancer vs non cancer patients 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%.

In order to further explore the lower rate of jaw osteonecrosis in non-cancer versus cancer patients, we combined the two cohorts of cancer patients and non-cancer patients who had received zoledronic acid in a Cox multivariable survival analysis of risk of jaw osteonecrosis. In preliminary analyses only patient gender was significantly associated with jaw osteonecrosis by log-rank test ($P < .001$). This was included in the Cox model, along with number of zoledronic acid infusions, and whether or not the patient had cancer. In these analyses, we removed patients who had six or more infusions, because the non-cancer cohort 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 (one to five) and gender. The confidence intervals 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 cancer patients, 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 total number of infusions. Those with non-cancer 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 non-cancer patients remained low compared to cancer patients (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. While this increased the estimated risk of jaw osteonecrosis, it did not

affect the large difference in the rates of the outcome between cancer and non-cancer patients. For example, when the outcome of jaw osteonecrosis was broadened to include any patient with at least one diagnosis of jaw osteonecrosis (ICD-9-CM 733.45), whether or not a procedure or imaging study was performed, the hazard of jaw osteonecrosis in non-cancer patients was 0.22 (95% CI; 0.12, 0.42), compared to cancer patients.

Discussion

There is little doubt that IV bisphosphonates can cause osteonecrosis of the jaw. This condition was exceedingly rare until the 1990's, when it became increasingly more common and almost entirely limited to cancer patients who had received IV bisphosphonates either to treat or prevent bone metastasis.^{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 clinical trials, but the algorithms to identify toxicities have important limitations. Prior 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.²⁴⁻²⁹ The ICD-9-CM code 733.45, "osteonecrosis of the jaw", was introduced only in 2007. Prior to 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.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 risk of jaw osteonecrosis.^{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 cancer and non-cancer patients, 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 cancer and non-cancer patients to an extent that could result in a six fold difference in 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,¹¹⁻¹⁴ reducing the likelihood of substantial numbers of undiagnosed cases.

As a comparison group, we included patients who had received a 30-day supply for an oral bisphosphonate prescription. We reasoned that these patients would be the most appropriate "non-treatment" 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 under age 65 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.¹⁰ These have not been reported in the randomized trials, but meta-analyses of case-control and cohort studies suggest the rate is lower than that reported for jaw osteonecrosis.^{3, 10}

A number of national organizations and authorities have recently decried the low treatment rates for osteoporosis, even in high risk patients with prior fractures.^{1, 3, 9} A case could be made that IV bisphosphonates are underutilized 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.^{1, 3} In a randomized controlled trial of zoledronic acid after hip fracture, Lyles et al.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 7,230 women with osteoporosis found a significant absolute reduction at three years of 7.6% in vertebral fractures and 0.9% in hip fractures.⁵ Absolute risk reductions increase with age^{32, 33} and with length of follow up.^{5, 34} These reductions compare to an absolute increase in risk of jaw osteonecrosis of 0.08% over six 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.¹⁴

Conclusion

There is growing concern about the preventable morbidity and mortality associated with untreated osteoporosis, especially in high risk patients such as those with prior fractures.^{1, 2, 10, 27, 28} Fear of jaw osteonecrosis is thought to be an important driver of that under treatment. Our data, combined with the results of prior studies, suggests that the risk of jaw osteonecrosis after IV bisphosphonate is considerably lower in patients with osteoporosis than in cancer patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Author contributions: **James S. Goodwin, MD:** conception or design; drafting of the manuscript; supervision; obtaining funding. **Jie Zhou, PhD:** acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis. **Yong-Fang Kuo, PhD:** acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; supervision; statistical analysis. **Jacques Baillargeon, PhD:** conception or design; critical revision of the manuscript for important intellectual content. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial support: Supported by grants [K05-CA134923, R24HS022134, P30-AG024832, ULI-TR001439], from US Public Health Service and from the Cancer Prevention and Research Institute of Texas (RP101207). Funders

had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; and in the decision to submit the manuscript for publication.

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Abbreviations used in the manuscript

CI	Confidence Interval
HMO	Health Maintenance organization
ICD-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
IV	Intravenous

Figure 1.

Kaplan-Meier survival free of jaw osteonecrosis for patients receiving oral bisphosphonate ≤ 30 days, along with cancer and non-cancer patients receiving 1-5 IV infusions of zoledronic acid.

Kaplan Meier survival free of jaw osteonecrosis for three cohorts 1) Those who received 1-5 IV infusions of zoledronic acid for a cancer; 2) Those who received 1-5 IV infusions of zoledronic acid for a non-cancer indication; and 3) Those who did not receive IV bisphosphonate but received a prescription for an oral bisphosphonate and took it for 30 days or less. The numbers of patients at risk in the three cohorts over time are given below the graph.

Table 1

Baseline characteristics for the patients given intravenous bisphosphonate for a cancer indication versus for a non-cancer indication, as well as patients receiving oral bisphosphonates for a month or less.

Patient Characteristics	Cancer (N = 11,098)	Non-cancer (N = 18,361)	Oral bisphosphonate users (N = 6,880)
Comorbidity			
0	5,462 (49.22%)	9,799 (53.37%)	3,385 (49.20%)
1	2,895 (26.09%)	5,063 (27.57%)	1,830 (26.60%)
2	1,434 (12.92%)	2,025 (11.03%)	807 (11.73%)
>= 3	1,307 (11.78%)	1,474 (8.03%)	858 (12.47%)
Medicaid eligible			
No	9,987 (89.99%)	16,329 (88.93%)	4,649 (67.57%)
Yes	1,111 (10.01%)	2,032 (11.07%)	2,231 (32.43%)
Age (years)			
65 <=, <=69	2,238 (20.17%)	3,165 (17.24%)	1,278 (18.58%)
70 <=, <=74	2,816 (25.37%)	4,102 (22.34%)	1,502 (21.83%)
75 <=, <=79	2,646 (23.84%)	4,346 (23.67%)	1,468 (21.34%)
80 <=, <=84	1,994 (17.97%)	3,803 (20.71%)	1,359 (19.75%)
>= 85	1,404 (12.65%)	2,945 (16.04%)	1,273 (18.50%)
Race/Ethnicity			
White	9,583 (86.35%)	16,695 (90.93%)	5,326 (77.41%)
Black	845 (7.61%)	547 (2.98%)	461 (6.70%)
Hispanic	427 (3.85%)	643 (3.50%)	745 (10.83%)
Others	243 (2.19%)	476 (2.59%)	348 (5.06%)
Gender			
Male	4,915 (44.29%)	1,021 (5.56%)	584 (8.49%)
Female	6,183 (55.71%)	17,340 (94.44%)	6,296 (91.51%)
Type of drug			
Etidronate	1 (0.01%)	3 (0.02%)	-
Ibandronate	93 (0.84%)	1,623 (8.84%)	-
Pamidronate	1,029 (9.27%)	155 (0.84%)	-
Zoledronic acid	9,482 (85.44%)	16,046 (87.39%)	-
More than 1	493 (4.44%)	534 (2.91%)	-
Number of infusions			
1 – 2	3,709 (33.42%)	12,304 (67.01%)	-
3 – 4	1,863 (16.79%)	4,339 (23.63%)	-
5 – 6	1,203 (10.84%)	865 (4.71%)	-
7+	4,323 (38.95%)	853 (4.65%)	-

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 infusions or fewer of zoledronic acid.

	Number of patients (total 21,546)	Hazard (95% CI) for jaw osteonecrosis
Number of infusions		1.10 (0.79-1.53)
Gender		
Male	3,197 (14.84%)	Reference
Female	18,349 (85.16%)	0.41 (0.14-1.17)
Indication for bisphosphonate		
Cancer	5,548 (25.75%)	Reference
Non-cancer	15,998 (74.25%)	0.17 (0.06-0.46)

CI: confidence interval.