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Zoledronate and other risk factors associated with osteonecrosis of the jaw in cancer patients: a case-control study

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Abstract

Background—Bisphosphonates (BPs) effectively treat metastatic bone disease, hypercalcaemia, and osteoporosis. BP exposure, however, may be associated with osteonecrosis of the jaws (ONJ). The aim of the present study was to estimate the magnitude of the association between intravenous BP exposure and ONJ, and to identify potential confounders.

Methods—Using a case-control study design, the investigators identified a sample of cases with ONJ and randomly matched them with five controls per case. The controls were matched to cases on age, sex, cancer type, and date of cancer diagnosis. The medical records were abstracted and data on BP exposure, cancer therapy and comorbidities were recorded. Statistical analyses were performed using conditional logistic regression in Stata 9.0.

Results—Thirty cases of osteonecrosis of the jaw (ONJ) were identified at Massachusetts General Hospital from February 2003 through February 2007. Zoledronate was found to confer significant risk towards development of ONJ (adjusted odds ratio = 31.8, $p < 0.05$). While a trend towards increased risk was noted for pamidronate, this association was not significant after controlling for zoledronate. Obesity, smoking, and metastasis were significantly associated with ONJ development, whereas oral bisphosphonates had no effect.

Conclusion—In this study, cancer patients who had received zoledronate exhibited a significant 30-fold increase in their risk to develop osteonecrosis of the jaw. More studies are needed to elucidate the exact role of obesity and smoking in the development of ONJ, and the complex interactions of IV bisphosphonates with other chemotherapies during cancer treatment.

Introduction

Bisphosphonates (BPs) are osteoclast inhibitors used for the management of **various types of osteolysis. Oral BPs are primarily used to manage osteoporosis. Intravenous (IV) BPs such as zoledronate and pamidronate are primarily used to treat hypercalcaemia, lytic bone lesions in multiple myeloma or metastatic bony lesions in solid tumors.**^{1–3} Zoledronate is the most potent IV bisphosphonate and it is primarily used in oncology. **While IV bisphosphonates have been used off-label in the management of osteoporosis to reduce fracture rates in osteoporotic women, recently zoledronate was approved for use in the management of osteoporosis as a one-per-year infusion, indicating a significant rise in its use for the management of millions of women with this disease.**⁴

Osteonecrosis of the jaw (ONJ) has become a major concern for cancer patients taking these drugs.^{5–10} Although an abundance of case series have been published on this topic since 2003,

there is currently inadequate scientific evidence through well controlled epidemiologic studies that explore the association between exposure and disease.

The purpose of this study was to assess the risk that intravenous (IV) BPs pose in the development of ONJ in cancer patients. We hypothesized that the use of IV BPs significantly increases the risk for ONJ. Secondary aims included the assessment of additional risk factors for ONJ development and the “construction” of a clinically relevant predictive model of disease.

Materials and Methods

Study design

The investigators designed and implemented a case-control study, which was reviewed and approved by the institutional review boards (IRB) of Harvard Medical School, Harvard School of Dental Medicine, and Massachusetts General Hospital (MGH).

Sample

Eligible cases were patients diagnosed with cancer, met diagnostic criteria for ONJ, and had been treated from February 2003 through February 2007 at Massachusetts General Hospital (MGH) in Boston. Cases were found via international classification of disease (ICD-9) diagnostic code and current procedural terminology (CPT) code searches within the front-end anonymized electronic medical record search software program at MGH (Research Patient Database Query Tool - RPDQ). ICD-9 diagnostic codes for necrosis of the jaw (526.4), chronic osteomyelitis (730.1) and avascular necrosis (733.40) and CPT codes for excision of mandibular bone (21025) and excision of facial bone(s) (21026) were used to identify potential cases. To qualify as a case, subjects needed to have documented evidence in clinician progress notes of exposed bone in the maxillofacial region for more than 8 weeks, and no history of radiation therapy to the maxilla or mandible. Subjects were excluded as cases if they had malignant bony metastases to the jaws.

For each case, a pool of controls was returned using an RPDQ search matching same sex, age (± 5 years), same cancer type, and year of cancer diagnosis. Thus controls were cancer patients matched in the selection criteria (age, sex, cancer type and year), had no evidence of ONJ, and had received oncologic care at the MGH or Dana Farber Cancer Institute (DFCI). **Five controls were randomly selected for each case among those who met the match criteria for each case.**

Study variables

The primary predictor variable was intravenous BP exposure. For subjects receiving zoledronate or pamidronate, data were collected on dose, number of infusions, and number of months from initial to most recent infusion. The investigators calculated cumulative BP exposure (mgs) for zoledronate and pamidronate using information from MGH medical records and estimates of BP exposure from outside institutions. **We also searched the medical records for information on Oral BP use and recorded it as a separate variable, coded as “any oral BP use” or “none”. Because oral BPs may not be routinely given to cancer patients, we could not identify information about the dose or duration of use for oral BPs.**

Demographic variables included age, sex, cancer diagnosis, and year of cancer diagnosis. Stage was recorded based on Tumor, Metastasis, Node (TMN) Classification system for solid tumors. Multiple myeloma was staged using the Durie-Salmon system. If multiple stages were listed in the patient’s medical record, the most advanced stage was used for analyses. Metastasis,

recorded as a binary variable, i.e. present or absent, was defined as involvement of bone or soft tissue not of primary origin.

Medication use was recorded as a binary outcome for cancer chemotherapy, oral BP use, statin use, and steroid use. Data for each type of cancer chemotherapeutic agent was recorded. Steroid use was divided into high and low dose. High steroid use was defined as pulse therapy for cancer treatment (40mg of dexamethasone for 4 days every 4 weeks, or 60mg or higher of prednisone). Low steroid use was any exposure to steroids which did not meet the threshold for high steroid use.

Comorbidities were recorded as a binary outcome based on positive clinical diagnosis. Obesity was defined by a BMI of 30 or higher post cancer diagnosis. Being a smoker was defined by a positive history of smoking within 5 years of cancer diagnosis. Cumulative smoking history was recorded in pack years using the most recent estimate available.

Data collection and analyses

Data sources were the subjects' electronic and paper medical records. Data were compiled using a data abstraction form. Statistical analyses used conditional logistic regression in Intercooled Stata 9 software (Stata) to estimate the risk of ONJ and to compute odds ratios, p-values, and 95% confidence intervals. Conditional logistic regression takes into account the matching variables "age", "sex", "cancer diagnosis", and "date of cancer diagnosis". Descriptive statistics, bivariate, and multivariate statistics were computed. Initially we used the univariate logistic regression function to test each independent variable separately and calculated the crude risk of ONJ for each specific factor. Based on the findings of the univariate crude statistics, we selected those variables that were significant at $p < 0.05$ for further analyses. We subsequently used multivariate conditional logistic regression to calculate the risk of ONJ for IV BP users, as well as to test the association with various confounders that were found significantly associated with ONJ in the previous step. The preliminary multivariate model was $Y_i = b_0 + b_1 (\text{Zoledronate}) + b_2 (\text{Pamidronate}) + b_3 (\text{oral BP}) + b_4 (\text{alcohol}) + b_5 (\text{asthma}) + \dots + b_j (\text{Comorbidities in Table 4}) + b_k (\text{specific chemotherapeutic agents})$, after adjusting for the matched design variables.

All modeling was performed manually (without stepwise regression functions). The final predictive model was composed of candidate variables which exhibited p-values < 0.05 in the multivariate analysis (zoledronate, smoking and obesity) and biological relevance (presence of metastasis). **As a final step, the investigators tested each of the non-significant covariates against the final predictive model. While this final step added information about the adjusted risk of each non-significant variable, the final model remained robust and the estimates of the three significant variables, namely zoledronate, obesity and smoking did not differ significantly.**

Results

Ninety-five potential cases were identified using the wide ICD-9 and CPT search via RPDQ. Electronic medical records were reviewed for each potential case. Sixty-seven cases were rejected due to osteonecrosis in a site other than the mandible or maxilla. An additional two cases were identified by electronic progress notes review while adjudicating suitable controls. In those two cases, ONJ had not been coded within the MGH system because the diagnosis and management occurred at an outside facility. Four ONJ cases had incomplete BP dosing information and were excluded from all BP analyses. These cases were receiving oncologic care at an outside institution, but were referred to MGH for management of ONJ. The final

sample of cases was composed of 30 subjects with ONJ diagnosed between 2/03–2/07 with a mean age of 65±12 years; 50% (15) were males (see Table 1).

The distribution of primary malignancies among ONJ cases was as follows: four prostate carcinomas, eleven breast, two lung, one kidney cancer and twelve multiple myelomas. The ONJ group experienced significantly more advanced disease, with twice as many cases with metastasis (93.1%) compared to the control group (47.3%, $p < 0.001$). Metastases was a significant predictor of ONJ risk (OR = 41.0, C.I: 5.3–315.3) in the crude analysis, and remained a strong but marginally significant predictor in the adjusted analysis, (OR=27.4, CI: 0.9–757.4) when controlling for zoledronate, obesity, and smoking. While the p-value for “metastases” was less than 0.05 ($p=0.051$) in the multivariate analysis, the investigators decided to include it in the final model due to its biologic significance and the potential to control for many unmeasured confounders associated with advanced cancer.

ONJ cases had significantly higher rates of bisphosphonate use; Table 2 summarizes the crude and adjusted odds ratios and confidence intervals. Oral bisphosphonates were not associated with increased risk. Pamidronate exposure was significantly higher in the ONJ group than in the controls ($p < 0.01$), but this association was not significant after controlling for zoledronate. Positive history of zoledronate use was associated with high levels of increased risk in both crude analysis (OR = 71.1, 95% C.I: 9.4–534.8) and adjusted (OR=31.8, 95% C.I: 1.7–579.3); all measures of zoledronate exposure were associated with significant elevation of ONJ risk (mgs, months of exposure, and numbers of infusion). **In the multi-variate analysis the effect of zoledronate was adjusted for the use of pamidronate. However, pamidronate was not statistically significant. Further, the OR of zoledronate did not differ significantly (change less than 10%) between the two different models, the one with pamidronate and the one without. Thus, to be consistent with the statistical methodology we chose not to include pamidronate in the final model. For users interested to see the effects of pamidronate, tables x and x present the crude and adjusted odds ratios.**

When examining the covariates, several chemotherapeutic agents were associated with increased risk in the **univariate** crude analyses, including capecitabine (OR = 19.5, 95% C.I: 2.2–171.0), gemcitabine (OR = 6.2, 95% C.I: 1.5–25.6), paclitaxel (OR = 6.3, 95% C.I: 1.4–27.3), low dose of steroids (OR = 3.2, 95% C.I: 1.4–7.7), and vinorelbine (OR = 23.4, 95% C.I: 2.7–199.3) (see Table 3).

Among the various co-morbidities that we evaluated, two were found to be associated with significantly increased risk: obesity (OR = 4.0, 95% C.I: 1.7–9.0) and smoking (OR = 5.9, 95% C.I: 2.2–15.4) (see Table 4). The risk of ONJ was significantly increased with each pack year of smoking (OR = 1.04, $p < 0.01$, 95% C.I: 1.01–1.06).

The final conditional logistic regression model consisted of the following variables: metastases; zoledronate; obesity; and smoking (see Table 5). The final step in our statistical analyses was to re-evaluate the effect of each non-significant covariate against the final model. All drug and cancer therapeutic agents were no longer significant, although pamidronate (OR=2.8, $p = 0.19$, 95% CI: 0.6–14.0), paclitaxel (OR= 23.5, $p = 0.157$, 95% C.I 0.3–1827.8), trastuzumab (OR= 67.9, $p = 0.12$, 95% C.I 0.4–13140.0), and vinorelbine (OR= 109.6, $p = 0.10$, 95% C.I 0.4–31679.4) use were suggestive of increased risk.

Discussion

This is the first hospital-based case-control study to report on the association between zoledronate use and osteonecrosis of the jaw in cancer patients while controlling for the effects of several known or potential confounders.

Because ONJ is a rare disease, we selected to study cancer patients as the referent population due to their propensity to receive intravenous bisphosphonates as part of their treatment plan. We were able to identify 30 cases of osteonecrosis of the jaw and 150 controls within a large referring hospital, the Massachusetts General Hospital. This sample size was adequate to study large risks such as the one proposed for zoledronate. However caution is required when interpreting the findings for many variables we evaluated due to the possibility of **Type I** error.

The primary aim of this study was to assess the relationship between intravenous bisphosphonate use and osteonecrosis of the jaw, controlling for other known or hypothesized confounders. **While IV BP use was associated with a 4-fold increase of risk in the bivariate analysis and a 29-fold increase of risk in the multivariate analysis, it is primarily zoledronate that** remained a strong and significant predictor of ONJ risk after taking into consideration (controlling for) the effects of various chemotherapies and medical conditions. Our results seem to indicate that zoledronate independently increased the risk for this serious adverse effect; individuals on zoledronate had a 30-fold increase in their risk to develop ONJ. ONJ patients treated with zoledronate received significantly higher doses than controls, and for prolonged periods of time.

Pamidronate was associated with a 3.8-fold increase in risk in the crude analysis ($p < 0.05$) and 2.8-fold increase in risk of ONJ in the adjusted analysis (non-significant). Of the 30 ONJ cases, 4 had only received pamidronate, 16 had only received zoledronate and 10 had received pamidronate followed by zoledronate. While it is important to note that pamidronate seems “capable” of producing ONJ in this dataset, we observed a clear distinction in its risk profile from the risk profile of zoledronate. One of the reasons that the two might have different risk profiles may be related to differences in their chemical structure and potency; indeed zoledronate appears significantly more potent than pamidronate in the literature. While pamidronate has been used extensively in the past, interestingly, the first case reports of ONJ were published only after zoledronate was marketed.

The use of oral bisphosphonates do not seem to increase the risk of ONJ. Several case series have linked oral BP administration to osteonecrosis of the jaws, suggesting that oral BPs alone increase ONJ risk. Our study found neither oral BP use nor osteoporosis to be suggestive risk factors.⁷ This findings agrees with observations from dental clinical trials that oral BPs do not seem to produce an adverse effect.

Our results corroborate with other studies indicating that IV BPs are risk factors for the development of ONJ, especially zoledronate.^{11–13} Non-BP risk factors identified in other studies included dental extractions¹², increasing age at diagnosis of cancer¹², and thalidomide¹¹. This study did not find thalidomide to increase risk, nor was it suggestive of increasing risk. We found 15 (50%) ONJ cases had extractions prior to diagnosis and one case (3.3%) had a dental implant placed prior to diagnosis. ONJ developed spontaneously in the remaining 14 (46.7%) cases. We were unable to perform bivariate analysis as extractions and implants were never reported in the control records.

Along with their anti-osteolytic function, bisphosphonates have been shown to have anti-angiogenic effects.^{15–17} Both properties are needed to control cancer metastasis to the bone, and indeed, metastasis is an indication for bisphosphonate therapy. It is thus expected to encounter higher rates of BP use among patients with metastasis. In this study, presence of cancer metastases was found to increase the risk of ONJ. While controls were matched to cases for cancer type and date of cancer diagnosis, we did not match for the presence of metastasis. However we used “metastasis” in our multi-variate model to control for any unmeasured confounding that this variable might “carry”. There may still be unresolved issues in cancer

biology that might interact in the development of osteonecrosis of the jaws, which must be evaluated further.

Smoking was found significantly associated with ONJ. Smoking has been linked with effects to every organ system in the human body. In the oral cavity, carcinogens in smoking delay wound healing and worsen periodontal disease^{18–22}, as well as promote soft tissue epithelial changes and cancer. In addition to affecting healing, nicotine in smoking may cause increased vasoconstriction in bone, leading to ischemic states that may underlie the pathophysiology of osteonecrosis.^{23–25}

Obesity was also found associated with ONJ risk in this group of cancer patients. While it is currently unclear what is the pathway that might cause an obese person to develop ONJ, several hypotheses can be proposed. **As steroid use is frequently associated with substantial weight gain, one such hypothesis is linked to prolonged steroid use. If obese cancer patients survive longer than others who lose weight during cancer treatment, then their probability of receiving higher doses of other chemotherapeutics or steroids also increases. While we controlled for use of steroids (coded as a binary, ‘yes/no’ variable), it is unclear if the obesity-ONJ association observed in this study is confounded by the total amount of time of steroid use.** In addition, it is unclear if obesity is potentially correlated with an increase in masticatory function that might lead to micro-traumas in hard tissues that are already compromised. Biochemical pathways that involve complex interactions of hormones and medications cannot be excluded. Interestingly, obesity seems to be inversely related to the development of osteoradionecrosis²⁶.

While a dose-response was observed, which might infer that zoledronate causes ONJ, case-control studies cannot establish causality. This study documented an association or a strong relationship between zoledronate use and osteonecrosis of the jaws that requires further evaluation. As ONJ is a rare occurrence, systematic pharmacogenetic studies are needed to assess the possibility of genetic susceptibility.

Conclusion

We documented a strong, significant and independent increase in the risk to develop osteonecrosis of the jaws in cancer patients who have received infusions of zoledronate. In this case-control study, individuals on zoledronate had a 30-fold increased risk to develop ONJ, and the risk seems to increase by 10% with each infusion. Smoking, obesity and metastases are additional risk factors that must be taken into account. Patients with multiple risk factors receiving BPs should be screened vigorously for early signs of disease.

Acknowledgements

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Table 1

Descriptive statistics of study population stratified by ONJ case or Control status

Study Variable	ONJ Case (n ₁)	Control (n ₂)
Sample Size	30	150
Sex (Males, n ₁ or n ₂) (%) [*]	15 (50)	75 (50)
Age (mean, sd)	65.0 ± 12	66 ± 11
Cancer to BP time in months (mean, sd)	63 ± 67	40 ± 49
Cancer Diagnosis, n (%)		
Prostate	4 (13.3)	20 (13.3)
Breast	11 (36.7)	55 (36.7)
Multiple Myeloma	12 (40)	60 (40)
Lung	2 (6.7)	10 (6.7)
Kidney	1 (3.3)	5 (3.3)
Cancer Stage, n, (% with stage 4 disease)		
Prostate	4 (100)	3 (15)
Breast (n ₁ =11, n ₂ =47) ^{**}	10 (91)	6 (13)
Multiple Myeloma (n ₁ =1, n ₂ =15) ^{‡**}	1 (100)	10 (67)
Lung (n ₂ =9) ^{**}	2 (100)	4 (44)
Kidney	1 (100)	3 (60)
Metastasis (n ₁ =29) ^{**}	27 (93.1)	71 (47.3)

* n (%) = sample size (% of sample)

** When data are missing, the available sample size is reported in parenthesis

[†] Cases and controls were matched[‡] Percent with Stage 3 disease

Table 2

Bisphosphonate use and risk of ONJ.

Bisphosphonate	Crude		Adjusted [†]	
	Odds Ratio	95% C.I	Odds Ratio	95% C.I
IV Bisphosphonate	4.23 [*]	2.21 – 6.25	29.77 [*]	1.20 – 733.91
Pamidronate: yes [‡]	3.85 [*]	1.41 – 10.51	2.88	0.59 – 14.03
per mg	1.00	0.99 – 1.00	1.00	0.99 – 1.00
per month	1.02	0.99 – 1.04	1.01	0.97 – 1.06
per infusion	1.02	1.00 – 1.05	1.02	0.98 – 1.07
Zoledronate: yes	71.16 [*]	9.47 – 534.88	31.82 [*]	1.75 – 579.33
per mg	1.03 [*]	1.02 – 1.04	1.04 [*]	1.01 – 1.06
per month	1.10 [*]	1.05 – 1.15	1.09 [*]	1.02 – 1.17
per infusion	1.12 [*]	1.06 – 1.17	1.11 [*]	1.03 – 1.20
Oral Bisphosphonates	0.33	0.07 – 1.65	1.26	0.11 – 14.86

* p<0.05

[†] adjusted for metastasis, obesity, and smoking[‡] further adjusted for zoledronate

Table 3

Chemotherapy and risk of ONJ.

Cancer and Chemotherapy	Crude		Adjusted [†]	
	Odds Ratio	95% C.I	Odds Ratio	95% C.I
Bevacizumab	5.00	0.70 – 35.50	2.83	0.02 – 463.35
Bone Marrow Transplant	0.63	0.14 – 2.84	0.69	0.10 – 4.62
Busulfan	1.49	0.28 – 7.93	0.50	0.05 – 5.12
Capecitabine	19.56*	2.24 – 171.02	1.08	0.07 – 16.42
Carboplatin	2.76	0.29 – 26.53	4.66	0.00 – 5.08e+08
Cyclophosphamide	0.77	0.30 – 1.98	0.79	0.17 – 3.67
Docetaxel	5.79	0.91 – 36.92	0.70	0.00 – 10801.39
Doxorubicin	0.90	0.30 – 2.74	0.54	0.09 – 3.34
Etoposide	2.24	0.11 – 44.88	0.48	0.00 – 43839.61
Gemcitabine	6.22*	1.50 – 25.68	2.87	0.17 – 48.50
Interferon	0.80	0.08 – 8.04	0.02	0.00 – 97805.93
Melphalan	0.77	0.23 – 2.63	0.56	0.11 – 2.81
Methotrexate	0.42	0.05 – 3.90	0.62	0.02 – 23.71
Paclitaxel	6.34*	1.47 – 27.34	23.54	0.30 – 1867.83
Statin	1.66	0.70 – 3.96	2.26	0.60 – 8.52
Steroid High Dose	0.35	0.10 – 1.22	0.56	0.08 – 3.81
Steroid Low Dose	3.28*	1.44 – 7.51	0.72	0.18 – 2.84
Tamoxifen	1.73	0.38 – 7.74	0.88	0.05 – 16.59
Thalidomide	2.40	0.68 – 8.54	1.97	0.39 – 10.04
Trastuzumab	2.50	0.23 – 27.57	67.95	0.35 – 13140.06
Vinorelbine	23.40*	2.75 – 199.31	109.70	0.38 – 31679.47

* p<0.05

[†] adjusted for metastasis, zoledronate, obesity, and smoking

Table 4

Comorbidities and risk of ONJ.

Comorbidities	Crude		Adjusted [†]	
	Odds Ratio	95% C.I	Odds Ratio	95% C.I
Alcohol Abuse	3.75	0.84 – 16.76	0.13	0.00 – 10.22
Asthma	1.73	0.60 – 5.00	1.17	0.18 – 7.55
Deep Vein Thrombosis	2.14	0.55 – 8.29	0.33	0.02 – 6.66
Diabetes	2.26	0.88 – 5.84	1.68	0.40 – 6.99
Gastric Reflux	0.94	0.39 – 2.25	0.92	0.17 – 4.97
Hypercholesterolemia	1.32	0.54 – 3.23	1.50	0.33 – 6.83
Hypertension	1.74	0.74 – 4.08	1.17	0.31 – 4.37
Obesity	4.02*	1.79 – 9.03	16.61*	1.80 – 153.71
Osteoporosis	0.70	0.21 – 2.35	2.26	0.29 – 17.65
Smoking: yes	5.94*	2.28 – 15.49	7.41*	1.28 – 43.10
per pack year	1.04*	1.01 – 1.06	1.03	0.97 – 1.10
Metastasis	41.09*	5.35 – 315.38	27.39*	0.99 – 757.40

* p<0.05

[†] adjusted for metastasis, zoledronate, obesity, and smoking

Table 5

Results from predictive multivariate logistic model (odds ratios and 95% confidence intervals)

Risk Factor	Odds Ratio	95% C.I	P-value
Zoledronate: yes	31.82	1.75 – 579.33	0.019
per mg	1.04	1.01 – 1.06	0.011
per month	1.09	1.02 – 1.17	0.009
per infusion	1.11	1.03 – 1.20	0.010
Smoking	7.41	1.28 – 43.10	0.026
Obesity	16.61	1.80 – 153.71	0.013
Metastasis	27.39	0.99 – 757.40	0.051