Osteonecrosis of the Jaw Onset Times Are Based on the Route of Bisphosphonate Therapy

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Purpose: Osteonecrosis of the jaw (ONJ) has been reported to be associated with patients receiving bisphosphonate (BP) therapy. There are many reports that suggest that the time of exposure to BPs is a significant risk factor for ONJ and that the greatest risk occurs after dentoalveolar surgery. The aim of this study was to retrospectively investigate the duration of BP therapy and related events before the onset of ONJ based on an intravenous (IV) or oral route of administration.

Materials and Methods: We conducted a retrospective cohort study of patients referred to our institution to identify the onset of ONJ based on the exposure to BP therapy and associated triggers (ie, dentoalveolar surgery or spontaneous occurrence) based on the route of BP administration. Demographic data (ie, age, gender, and race), medical diagnosis related to BP therapy, and information as to whether the BP therapy was continued at the time of ONJ diagnosis were also collected.

Results: We reviewed the records for 114 patients with a history of ONJ. We divided patient cohorts by route of BP administration, with 76 patients having a history of IV BP therapy and 38 patients having a history of oral BP therapy. The overall onset of ONJ was earlier in the IV BP group (median, 3 years) compared with the oral BP group (median, 5 years). There was no statistical difference in the duration to occurrence of ONJ associated with dental extraction compared with spontaneous occurrence for both the IV and oral BP groups.

Conclusions: The median onset of ONJ for patients undergoing IV BP therapy occurs earlier than the median onset for patients undergoing oral BP therapy, and there was no difference in onset occurring spontaneously and after dental extraction. The significance of these findings suggests that patients who receive IV BP therapy should be closely evaluated after the initiation of BP therapy. The lack of evidence suggesting greater onset after dental extraction may provide clinical support for dentoalveolar surgery that is indicated for patients with a history of BP therapy. Research focusing on the clinical circumstances and physiologic events during early antiresorptive therapy may provide insight as to the critical risk factors.

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Bisphosphonates (BPs) are widely used for the prevention and treatment of osteoporosis[1] and skeletal complications associated with metastatic cancer and multiple myeloma.[2] These drugs may also play a role in improving quality of life, preventing bone loss associated with chemotherapy, cancer prevention, and improved survival.[2-9] BP-related osteonecrosis of the jaw is most frequently defined as current or previous treatment with a BP, exposed bone in the maxillofacial region for more than 8 weeks, and no history of radiation therapy to the jaws.[10] However, a universally agreed upon definition for BP-related osteonecrosis of the jaw has not been established,[11,12] and the term osteonecrosis of the jaw (ONJ) may be more accurate when considering the occurrence of osteonecrosis associated with non-BP medications.[13-17] Although the pathogenesis is not well understood, suggested risk factors have included BP administration (ie, type, dose, and duration), local risk factors, and/or systemic risk factors. The complexity of this condition is even more apparent when considering the growing reports of ONJ without antiresorptive therapy and the controversies regarding the impact of infectious and aseptic inflammatory processes.[18-23]

ONJ has become a prominent enigma in the dental and medical communities. The number of cases reported has grown significantly since 2006 and could rise exponentially over the coming years.[24,25] The complexity of this condition is best illustrated by the various reported definitions, clinical descriptions, radiographic appearances, paucity of data, and numerous hypotheses regarding the pathophysiology.[26] Concerns about ONJ may have a broad health impact. Dilemmas arise because discontinuing BP therapy before dental procedures does not prevent[27,28] or improve ONJ,[29,30] and poor oral hygiene (or periodontal disease) may not correlate with risk assessment.[31] Patient management is further complicated because recommendations have focused on avoiding dental extractions,[11,32] whereas other reports suggest that ONJ may be triggered by infection.[33]

Although the incidence of ONJ is greater among patients who receive IV BP therapy,[34] previous reports suggest that the time of exposure to BPs and the number of infusions are the most significant risk factors for development of ONJ,[35-37] which is an important consideration in making treatment decisions.[38] One limitation with many studies that examine duration of BP therapy and onset of ONJ is the limited follow-up necessary to draw final conclusions.[39] The relatively small number of ONJ cases associated with oral BPs makes understanding risk particularly challenging.[40] This has led to a paucity of data that accurately identify onset based on the route of BP therapy. This information would be important to improve risk assessment and to determine the significance of associated triggers. We hypothesize that patients undergoing IV BP therapy have a different time to onset compared with patients who receive oral BP therapy. The primary objective of this investigation was to examine patients with ONJ and identify the relation between the duration of BP therapy and the onset of ONJ based on the route of BP administration. The secondary objective was to identify a trigger for the onset of ONJ.

Methods and Methods

DATA COLLECTION METHODS

To address the research objectives, we designed and implemented an institutional review board–approved retrospective chart review of patients referred to our institution for treatment of ONJ between 2008 and June 2011. The study population included all patients who had a history of BP therapy. We excluded patients who, on initial presentation, were diagnosed with ONJ but in whom subsequent biopsy confirmed other pathology (eg, metastatic malignancy, squamous cell carcinoma, cemento-osseous dysplasia, or odontogenic cysts). We developed 2 patient cohorts based on the route of BP administration (ie, oral or IV). For each patient cohort, we collected data related to the medical history (ie, medical diagnosis that necessitated BP therapy), demographics (eg, age at onset, gender, and race), and clinical events, as described by the subject, associated with the onset of ONJ (eg, duration of BP therapy, denture use, dental infection, extraction, and implant placement). The primary outcome variable was the duration of BP exposure before the onset of ONJ for the 2 cohorts. The secondary outcome variable was whether ONJ onset was associated with dentoalveolar surgery (eg, extraction or dental implant) or occurred spontaneously for the 2 cohorts. Diagnosis of ONJ was based on the American Association of Oral and Maxillofacial Surgeons definition and other clinical and radiographic criteria that have been reported where dental etiology could be excluded (ie, fistula, neurosensory changes, osteolysis, sequestrum formation, and osteosclerosis).[10,41-44]

STATISTICAL ANALYSIS

A descriptive analysis was performed on all demographic and predictor variables, and differences between the IV and oral administration groups were assessed with the t test (for continuous measures) and an exact Pearson χ^2 (for categorical measures). Initially, individual univariate Cox proportional hazards models were used to assess the relationship between the time receiving BP before the development of ONJ and each potential predictor variable. A multivariate Cox proportional hazards model was then created by use of all predictors with $P < .10$ in the univariate analyses. A subset analysis of the relationship between time to event and diagnosis was then undertaken in the IV administration group by use of a Kaplan-Meier analysis and log-rank tests.

Results

We collected data for 76 patients with a history of intravenous (IV) BP therapy (71% female and 29% male patients) and 38 patients with a history of oral

BP therapy (97% female and 3% male patients). Demographics and potential covariates are summarized in Table 1, grouped by route of BP administration. The groups differed statistically by age, gender, and race, with the oral group tending to be older, to have a higher proportion of female patients, and to have fewer white patients with more Asians. There was no statistically significant difference in terms of potential triggers of ONJ. The difference in gender is expected because the majority of the oral group was given BPs for osteoporosis prevention. Dental work was coded to a binary indicator of spontaneous versus after extraction, because there were insufficient numbers of subjects with specific conditions (eg, spontaneous with dentures and spontaneous with infection) to evaluate the effect at a more complex level. The majority of patients with spontaneous ONJ for both groups did not have any clinical history associated with a trigger (73%). Among the spontaneous cases for both groups, 10% were reported by patients to be associated with malfitting dentures, 10% were reported by patients to be associated with infected teeth, and 7% were associated with old implants (ie, placed before BP therapy).

The results of univariate Cox proportional hazards models for each potential predictor variable fitted separately to evaluate its relationship to duration of BP exposure is shown in Table 2. Gender and route of administration show statistically significant relationships to BP duration, with higher hazard rates in male patients and in patients undergoing the IV administration route. Age shows a trend toward a relationship with hazard increasing with age. A multivariate Cox proportional hazards model was then constructed with all predictor variables with $P < .1$ in the univariate models.

Table 3 shows the results of the multivariate Cox model, including age, gender, and route of administration. Age was not a statistically significant predictor of duration. Route of administration was statistically significant, with the hazard rate in the IV administration group being 1.796 times greater than the hazard rate in the oral administration group. Gender was also statistically significant, with a higher hazard rate in male patients. However, given the relationship of route of administration and gender, it is unclear whether the hazard ratio is the result of a real effect or a confounding of the effect of route of administration. Thus, after we adjusted for age and gender, the IV route of BP administration is statistically associated with a more rapid onset of ONJ than the oral route. Kaplan-Meier survival curves for the 2 administration route groups are shown in Figure 1. The median time to event in the oral administration group was 5 years (95% confidence interval, 3.79-6.21), and in the IV

Table 1. DEMOGRAPHICS AND POTENTIAL PREDICTOR VARIABLES BY ADMINISTRATION ROUTE

	IV BP (n = 76)	Oral BP (n = 38)	*P* Value
Age	61.3 (10.3)	74.2 (9.7)	<.001*
Gender	54 female/22 male	37 female/1 male	.002†
Race			
Asian	2 (3%)	8 (21%)	.004†
African American	8 (11%)	4 (11%)	
Indian	0 (0%)	1 (3%)	
White	66 (87%)	25 (66%)	
Hispanic ethnicity	11	4	.849†
Dental work	35	20	.555†
Drug holiday before ONJ	7	5	.530†
Diagnosis			
Osteoporosis	0	36	—
Multiple myeloma	22	0	
Cancer	54	2	

*Comparison by *t* test.
†Comparison by exact Pearson χ^2.

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Table 2. UNIVARIATE COX PROPORTIONAL HAZARDS MODELS (SEPARATE MODEL FOR EACH VARIABLE)

	Hazard Ratio	Wald Statistic	*P* Value
Age	0.987	2.940	.086
Gender	2.143	10.07	.002
Race	—	1.132	.769
Ethnicity	0.875	0.234	.629
Route of administration	2.004	11.637	.001
Dental work	1.097	0.243	.622
Drug holiday	0.889	0.149	.699

NOTE. Reference categories are female gender, non-Hispanic, oral administration, spontaneous ONJ occurrence, and no drug holiday.

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Table 3. MULTIVARIATE COX PROPORTIONAL HAZARDS MODEL

	Hazard Ratio	95% Confidence Interval
Age	1.000	0.982-1.019
Gender	1.676	1.022-2.749
Route of administration	1.796	1.095-2.946

NOTE. Reference categories are female gender and oral BP administration route.

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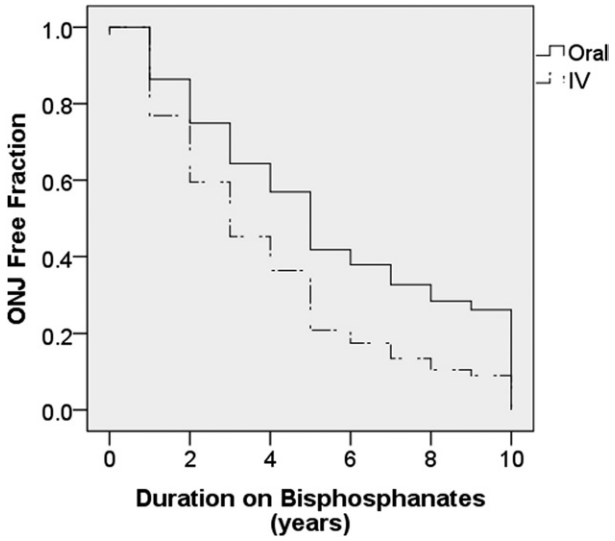

FIGURE 1. Survival curves for oral and IV administration route groups after adjustment for age and gender. The IV route group has lower ONJ-free fractions at all time periods than the oral route group.

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administration group, it was 3 years (95% confidence interval, 2.34-3.66).

A subset analysis was performed in the IV administration route group to evaluate the relationship between the diagnosis leading to BP therapy and the time to ONJ. A Kaplan-Meier survival curve analysis with diagnosis categorized as breast cancer, multiple myeloma, or other cancers (which were combined because of small numbers of each type) was performed (Fig 2). A log-rank test showed that the survival curves were statistically significantly different ($\chi^2 = 7.224$, $df = 2$, $P = .027$) with patients with other cancers having the fastest development of ONJ and multiple myeloma patients having the slowest. A post hoc analysis showed that only multiple myeloma and other cancers differed significantly ($\chi^2 = 8.254$, $df = 1$, $P = .004$). Breast cancer did not differ from other cancers ($\chi^2 = 3.018$, $df = 1$, $P = .082$), nor did breast cancer and multiple myeloma differ ($\chi^2 = 1.544$, $df = 1$, $P = .214$).

Discussion

This is the first case series that investigates the onset of ONJ based on the route of administration. We hypothesized that the route of administration would reflect different onset times. We found an earlier median ONJ onset for patients undergoing IV BP therapy compared with patients undergoing oral BP therapy. We also found that ONJ developed within the first 2 years in 40% of the patients in the IV BP group. Our data also illustrate that there is no difference in the ONJ-related trigger for either cohort.

The dichotomous ONJ onset times for patients undergoing IV and oral BP therapy may reflect the different pharmacologic properties of the drugs and/or the physiologic risk factors in the 2 groups.

PHARMACOLOGIC PROPERTIES

Over-suppression of bone remodeling is the leading theory as to the pathogenesis, and this is associated with a longer duration of exposure.[45] IV BPs are more potent than oral BPs, with greater mineral binding and greater suppression of bone turnover.[46] This may explain our data illustrating an earlier onset for the patients undergoing IV BP therapy. However, if over-suppression of bone remodeling was a significant factor in the pathogenesis of ONJ, it would be expected that osteonecrosis would be present throughout the skeleton and not confined to the jaws.[26] Therefore, the premise for over-suppression of bone remodeling leading to ONJ is based on the assumption that there is selective deposition of BPs in the jaws because of a faster bone turnover rate.[47] However, there is insufficient evidence that BPs accumulate at higher concentrations in the jaw (compared with other sites) or that bone remodeling of the jawbone is affected to a higher degree.[48-51] Indeed, there is compelling evidence that bone turnover is not reduced within ONJ lesions, which is shown by deep osteoclastic pits, the presence of osteoclasts, active bone resorption, and bone scintigraphy studies.[52] Although it may be argued that over-suppression is activated after dental extraction,[53] most of our patients had spontaneous ONJ develop. The fact that BPs become

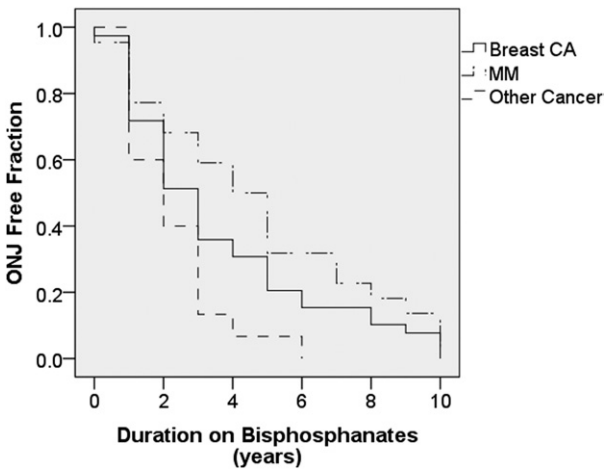

FIGURE 2. Kaplan-Meier survival curves for 3 diagnostic categories in IV administration group: breast cancer, multiple myeloma, and other cancers. The highest ONJ-free fractions occurred in the breast cancer group and the lowest in the other cancer group.

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buried in bone, where they do not affect bone turnover,[46,54] further challenges the over-suppression hypothesis.

SYSTEMIC AND LOCAL RISK FACTORS

Significant factors such as infection, biofilm, and inflammatory response[20,55-57] have been considered in the pathogenesis of ONJ and may reflect the greater immunologic, vascular, and osseous vulnerability during the early stages of cancer management in the IV BP group.[23] Furthermore, 1 or more of these factors may represent the critical trigger for the onset of ONJ. Tumor-induced immune suppression and the impact of chemotherapy (eg, compromised mucosal barrier or shift in oral microflora) may contribute to an acute physiologic "hit" facilitating oral infection[58-60] compared with the immunologic changes associated with osteoporosis.[61] Current research suggests that bacterial biofilms may play a significant role in the pathogenesis of ONJ[62-65] and present many clinical challenges because they are difficult to culture and antibiotic resistance may result in misguided antibiotic therapy.[65-67] A recent study suggests that there is a unique bacterial colonization associated with ONJ.[68] Moreover, half of these bacterial species in oral microbiome cannot be grown in the laboratory.[66,67] These noncultivable and sometimes dormant opportunistic pathogenic bacteria occupy different ecologic microniches and are likely involved in latent infections.[69-76] Similar studies with denosumab, which is used for both metastatic disease and osteoporosis (albeit with different dosing schedules) and has a relatively short half-life (ie, approximately 26 days),[77] may provide insight into the significance of comorbidities.

There have been numerous studies reporting variable durations of BP therapy before ONJ, which is usually associated with dental extractions. Dimopoulos et al[37] reviewed 15 patients with multiple myeloma in whom ONJ developed from 1995 to 2003 and was most commonly associated with dental extraction. They found a sustained increase in the risk of ONJ developing after 4 years of exposure to BPs and a median time to onset that was similar to ours, at 39 months. Bamias et al[35] reported an increasing cumulative hazard among 17 patients with multiple myeloma in whom ONJ developed from 1997 to 2003 and was most commonly associated with dental extraction. This study found a median time of onset of 20 months. Badros et al[36] reviewed 22 patients with multiple myeloma in whom ONJ developed from 2002 to 2005. They reported a 9% increase in the risk of ONJ with each decade of life and a 57% increase in the risk of ONJ with each year of time living with multiple myeloma. In most of their patients, ONJ developed after dental extraction with an increased onset, with a median time to onset of 8.4 years. Kos et al[78] reviewed 34 patients with oncologic disease and osteoporosis and suggested that the risk of ONJ was not related to total dose of BP received but most commonly occurred after dentoalveolar surgery. Hoff et al[79] reviewed 29 patients who had oncologic disease and were diagnosed with ONJ between 1996 and 2004. They identified duration of BP therapy and dental extraction as risk factors. The median time to onset for patients with breast cancer was earlier with zoledronate (3.33 years) compared with pamidronate (1.38 years); similarly, the median time to onset for patients with multiple myeloma was earlier with zoledronate (1.26 years) compared with pamidronate (1.59 years). Nicolatou-Galitis et al[80] examined 67 cancer patients and found the median duration of BP therapy preceding ONJ to be 36 months. They included patients with oral pain, periodontal disease, unexplained tooth mobility, and mastication difficulties of no obvious dental etiology. Lo et al[81] conducted a mail survey and found 9 patients diagnosed with ONJ after oral BP therapy. Of these ONJ cases, 5 occurred spontaneously and 4 occurred after dental extraction, and the median duration of BP therapy was 3.5 years.

Possible explanations for differences in our findings compared with these previous reports may be attributed to the greater number of patients enrolled, the diagnostic criteria for ONJ, differences in medical diagnosis (ie, metastatic cancer, multiple myeloma, or osteoporosis), and the longer time period over which these patients were studied.

One limitation of our investigation is that the frequency and number of doses of BP administration were not determined and/or varied for each patient during the course of therapy. Indeed, dose matching among various malignancies and BP drug schedules may not be feasible.[82] Although the groups were identified by route of administration, they also differed as to the drug administered and possibly the dosage and cumulative dosage. Very few patients had their BP therapy discontinued, and we cannot determine whether this factor affected the time of onset. It may be argued that this may play a role in the overall onset patterns. Other limitations include the different morbidities for the 2 cohorts and the accuracy in the recording of onset, especially with spontaneous ONJ lesions, which may go undiagnosed if asymptomatic or not associated with bone exposure. One confounding factor is that the oral administration group was older than the IV group, which may be expected because osteoporosis occurs later in life.

In summary, we found an earlier onset of ONJ for patients undergoing IV BP therapy compared with oral BP therapy, and there was no correlation to dentoalveolar surgery. The significance of these findings may facilitate research focusing on the clinical

circumstances and physiologic events during early antiresorptive therapy and may provide insight as to the critical risk factors. The lack of evidence suggesting greater onset after dental extraction may provide clinical support for dentoalveolar surgery that is indicated for patients with a history of BP therapy.

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