Original article

Title: Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: A cohort study

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Key words: alveolar bone loss; bisphosphonate; incidence; jaw; osteonecrosis; relative

risk; tooth extraction

Running title: Osteonecrosis of the jaw after tooth extraction

Abstract. The purposes of this study are to estimate cumulative incidence and risk ratio for osteonecrosis of the jaw (ONJ) after tooth extraction in patients with and without administration of bisphosphonates (BP) and to identify potential risk factors for bisphosphonate-induced osteonecrosis of the jaw (BIONJ). A cohort study was conducted in all patients undergoing tooth extraction at a university hospital in Japan from April 2006 to June 2009. Of 3216 patients, 126 had BP administration, of whom 5 (3.9%, 95% confidence interval (CI): 1.2 to 9.2) developed ONJ, versus 1 (0.032%, 95% CI: 0.00081 to 0.18) among 3090 patients without BP administration. BP administration was associated with the development of ONJ after tooth extraction, with an unadjusted risk ratio of 122.6 (95% CI: 14.4 to 1041.8). When stratified by age and route of BP administration, the risk ratio for ONJ patients aged 65 years or older with intravenous BP administration compared to those without was 200.2 (95% CI: 23.8 to 1679.4, $P < 0.001$). Patients receiving BP showed a significant association between the incidence of BIONJ and alveolar bone loss score. The risk of ONJ is higher in patients with than without BP administration, particularly intravenous administration. Severe periodontitis might be a risk factor for BIONJ.

Introduction

Bisphosphonates (BP) are used for the treatment of a range of bone involvement, such as osteoporosis or bone metastases of malignant cancer, and their efficacy in preventing further bone damage, reducing bone pain, and increasing bone mineral density has been confirmed. Nevertheless, in 2003 Marx reported bisphosphonate-related osteonecrosis of the jaw or bisphosphonate-induced osteonecrosis of the jaw (BIONJ), as a side effect of BP treatment[1]. However, the incidence and mechanism of BIONJ have not been accurately determined.

Since that initial report, the association between BP exposure and the incidence of osteonecrosis of the jaw (ONJ) has been clarified in several case series, reviews, epidemiologic studies and clinical trials[2-11], which reported a prevalence of BIONJ ranging from 0.7% to 18.6% on intravenous[5-7] and 0.01% to 4.3% on oral administration[8, 9]. Nevertheless, the low incidence of ONJ among BP-naïve patients has prevented any direct estimation of the risk ratio of ONJ among patients receiving BP. Black et al. indentified only 1 patient with possible ONJ among 3852 postmenopausal women during a 3-year period[10]. In their 6-year population-based cohort study using medical claims data, Wilkinson et al. found that 0.30% of naïve patients had been diagnosed with inflammatory conditions or osteomyelitis of the jaw but not ONJ[11].

Tooth extraction has been reported to be the main initiating factor and one of the most common risk factors for BIONJ among patients receiving BP (approximately 86% of cases) [8, 12, 13], and relative risk of BIONJ in these patients is 5.3 to 53 times higher than in BP patients who do not experience tooth extraction[5, 14, 15]. A current guideline recommends non-surgical treatment rather than tooth extraction in dental patients at high risk of BIONJ[16], but given that bacterial infection is itself reported as a critical risk factor for BIONJ[16], avoiding extraction might be problematic in cases in which the bacterial infection remains. Further, information on the incidence or risk factors for BIONJ after tooth extraction among patients receiving BP is limited. A better understanding of this condition, particularly with regard to risk factors and incidence, will be helpful to dentists in the care of patients receiving treatment with BP.

The purpose of this study was to estimate the cumulative incidence and risk ratio for ONJ after tooth extraction in patients with and without administration of BP, and to identify potential risk factors for BIONJ, including oral status.

Materials and methods

Study design and cohort

We conducted a retrospective analysis of patients who had undergone tooth extraction between April 2006 and June 2009 at the Department of Oral and Maxillofacial Surgery, Kyoto University Hospital. Patients were identified using administrative data, and dental and medical records were reviewed from January 2010 to August 2010. This study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine.

Definition and diagnosis of ONJ

Inclusion was restricted to patients aged 20 years or older. ONJ in this study was diagnosed by the presence of exposed bone in the maxillofacial region that had persisted for more than 8 weeks, in reference to diagnostic criteria formulated by the American Association of Oral and Maxillofacial Surgeons[16]. Diagnoses were determined independently by two oral and maxillofacial surgeons. Among patients undergoing tooth extraction at our institution, we excluded cases of tooth extraction in patients with metastatic tumors to the oral region; signs of osteomyelitis or exposed bone in the maxillofacial region before extraction; any history of craniofacial radiation therapy; and

patients for whom panoramic radiographs before extraction were not available. Cases with diagnostic disagreement were then discussed. Finally, ONJ cases with diagnostic disagreement were regarded as non-ONJ cases and analyzed with the non-ONJ patients. The kappa value for inter-observer agreement was 0.86 (95% confidence interval (CI); 0.82-0.89).

Data collection

For each chart reviewed, we collected the following information: demographics; medical history; test results; and potential risk factors associated with ONJ, namely the use of steroids, chemotherapy (including anticancer agents, immunosuppressive agents and thalidomide), current smoking status, current alcohol intake, diabetes, and details regarding BP treatment (indication, type, dose, duration). Recommended regimens for oral BP administration in the treatment of osteoporosis in Japan are etidronate sodium, 200 mg per day (Didronel ®); alendronate sodium, 5 mg per day or 35 mg per week (Fosamac® or Bonalon®); and risedronate sodium, 2.5 mg per day or 17.5 mg per week (Actonel® or Benet®), while those for intravenous administration in the treatment of osteolytic bone metastases of malignant cancer, multiple myeloma, or hypercalcemia of malignancy are incadronate, 10 mg per time (Bisphonal®); pamidronate, 30 - 45 mg for

hypercalcemia of malignancy, or 90 mg every 4 week for osteolytic bone metastases of malignant cancer (Aredia®); and zoledronic acid, 4 mg every 4 week (Zometa®). Intravenous BP have not been approved for osteoporosis in Japan.

For patients treated with BP in the hospital, we entered these medications into the electronic medical record system to obtain the type and duration of BP administration, and the number of patients administered them to estimate the incidence of BIONJ. For patients treated with BP in other hospitals, we reviewed the record of their first examination at our hospital, at which we recorded the type and duration of BP administration as obtained from the referring physician by letter.

Measurement of oral status

Using the patient's panoramic radiograph before tooth extraction, an experienced examiner calculated the DMF index and severity of alveolar bone loss. The DMF index, which comprises the number of decayed (D), missing (M), and filled (F) teeth, has been established as a key measurement of caries experience in dental epidemiology[17]. In addition, the severity of alveolar bone loss was measured to examine periodontal status as a percentage of missing bone at the mesial and distal surfaces of each tooth present[18]. Severity was estimated from (a-b)/a×100 (%) using the panoramic radiograph (a,

distance from radiographic apex to cement-enamel junction (mm); b, distance from radiographic apex to interproximal alveolar bone crest (mm)). If the location of the cemento-enamel junction was obscured by interproximal fillings, the cervical margin of these fillings was chosen as standard. If the cervical margin of these fillings was obscured, bone loss height was characterized as unmeasurable. Each tooth surface was assigned a score corresponding to a bone loss of 0% to 24%, 25% to 49%, 50% to 74%, and 75% to 100%, respectively. These measurements were then averaged to yield a single mean bone loss score for each patient, with a higher score indicating more severe periodontal disease[19].

Statistical analysis

The incidence of ONJ was calculated using the cumulative incidence method, which is defined as the number or proportion of a cohort of people who experience the onset of ONJ during a specified time interval[20]. In the calculation of the CI for incidence, the Poisson distribution was used. Medians for continuous variables were compared using the Wilcoxon rank-sum test. Proportions across levels of categorical variables were compared using the Fisher exact test. Risk ratios were calculated for all dichotomous variables and Wald CIs were calculated[20]. All *P* values were two sided at a significance

level of 5%. For missing data, available-case analysis was performed in addition to multiple imputation analysis. All statistical analysis was performed using Stata 11.2 software (Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

A total of 3240 patients underwent tooth extraction at our institute. After exclusion of 8 patients with a history of craniofacial radiation therapy and 16 without a panoramic radiograph, 3216 (99.2%) eligible patients were entered into the analysis. Patient characteristics are summarized in Table 1. A total of 126 patients (3.9%) had received BP; among the 103 women (81.7%), 86 (83.5%) were treated with oral BP and 17 (16.5%) with intravenous BP, while among the 23 men, 13 (56.5%) received oral and 10 (43.5%) received intravenous BP. Seven patients were diagnosed with both osteoporosis and breast cancer, all of whom had been treated with oral BP. The total number of patients without BP administration was 3090 (96.0%), of whom 51.8 % were women. Median age was lower (39.0 years) than that of patients with BP administration (66.0 years).

Cumulative incidence of ONJ after tooth extraction

Five of the 126 patients receiving BP developed ONJ (3.9%, 95% CI: 1.2 to 9.2), versus 1 (0.032%, 95% CI: 0.00081 to 0.18) of the 3090 without BP administration. Individual data of these 6 patients with ONJ are shown in Table 2. The cumulative incidence of ONJ among patients with BP administration was significantly higher than that among those without ($P < 0.001$). The crude risk ratio for ONJ after tooth extraction for patients with BP administration compared to those without was 122.6 (95% CI: 14.4 to 1041.8). By route of administration, cumulative incidence was 1.0% (95% CI: 0.025 to 5.6) among patients treated with oral BP and 14.8% (95% CI: 4.0 to 37.9) in those treated with intravenous BP. The risk ratio for ONJ was 31.2 (95% CI: 1.9 to 495.4) among patients treated with oral BP and 457.7 (95% CI: 52.8 to 3962.7) in those treated with intravenous BP. Large differences were seen in age and prevalence of cancer or osteoporosis between BP and BP-naïve patients. We therefore performed stratified analysis by age and route of BP administration to estimate risk ratios for ONJ to control for these factors. (Table 3). Among patients aged 65 years or older (median 73, range 65 to 94), the risk ratio for ONJ for patients with oral or intravenous BP administration compared to those without was 12.9 (95% CI: 0.82 to 204.6, $P = 0.138$) or 200.2 (95% CI: 23.8 to 1679.4, $P < 0.001$), respectively.

Association with possible risk factors for BIONJ after tooth extraction

We next investigated potential risk factors associated with BIONJ among patients with BP administration. The incidence of BIONJ was significantly associated with the type of BP (P = 0.007) but not with the other potential risk factors (Table 4). The crude risk ratio for intravenous compared with oral BP administration was 14.6 (95% CI: 1.7 to 125.8). The type, dosage and duration of intravenous BP administration is shown in Table 5. Median duration in patients with BIONJ (13.5, range: 7 to 49 months) was longer than that in patients without BIONJ (7.5, range: 1 to 96 months), but this difference was not significant. Regarding oral BP, etidronate, alendronate and risedronate were given as single agents to 4 (4.0%), 54 (54.5%), and 31 patients (31.3%), respectively, while the rest (10.2 %) received a series of double BP agents.

Regarding oral status among patients receiving BP, we found a significant association between the incidence of BIONJ and bone loss score but not DMF index. The median bone loss score among BIONJ patients was significantly higher than that among those without BIONJ (P = 0.024) (Table 4): namely, while median bone loss score among those without BIONJ was 1.3 (interquartile range 1.1 to 1.6) and the prevalence of severe periodontal status was 7.4%, median score among BIONJ patients

was 1.6 (interquartile range 1.5 to 1.9) and the prevalence of severe periodontal status was 20.0%. Similarly, this association was significantly found among patients aged 65 years or older (median, 1.4 vs. 1.6, $P = 0.034$).

Missing data

Potential risk factors were not available for eight patients, namely the duration of BP administration for one patient and current alcoholic intake and current smoking for seven patients. We therefore performed available-case analysis (Table 4 and Table 5). Additionally, we also performed multiple imputation analysis, but the results did not change from those of available-case analysis (data not shown).

Discussion

We found that the cumulative incidence of ONJ among patients who had received BP administration was significantly higher than that among patients who had not received this treatment (crude risk ratio 122.6, 95% CI: 14.4 to 1041.8). To our knowledge, this study is the first cohort study to evaluate the cumulative incidence and risk ratio for ONJ after tooth extraction among patients with or without BP administration. Additionally, risk ratio for ONJ was particularly elevated in the subpopulation of

patients with intravenous BP administration. Age–stratified analysis showed no significant association between the incidence of ONJ after tooth extraction and oral BP among elderly patients aged over 65 years old, but a significant association with intravenous BP administration (risk ratio 200.2, 95% CI: 23.8 to 1679.4). These results indicate that intravenous BP may be associated with an increased risk of ONJ after tooth extraction among elderly patients over 65 years old. Dental practice-based research network (DPBRN) reported an unadjusted odds ratio for ONJ for patients with oral BP administration compared to those without of 15.5 (95% CI: 6.0 to 38.7) in two health-care organizations, regardless of a history of tooth extraction[21]. The impact of oral BP on the risk of ONJ after tooth extraction requires further investigation.

In the DPBRN study, the investigators had so little hospital information that they could not estimate the risk ratio of intravenous BP[21]. In our study, although a single-center study, we were able to collect detailed BP administrative data from the hospital database and estimate the risk ratio stratified by the route of BP administration. In addition, oral and maxillofacial surgeons followed up all patients after tooth extraction, diagnosed ONJ, and excluded patients with non BP-induced ONJ. This extraction of detailed information and manual confirmation of ONJ likely improved the reliability of our results.

Previous studies have reported that preventative dental treatment decreased BIONJ risk among patients with intravenous BP administration[22-24]. All patients who consulted the outpatient clinic of our department before BP administration underwent an oral examination, screening for periodontal disease, and oral cleaning. For patients receiving BP, particularly intravenous BP, an extensive oral examination was performed and preventive dental treatment was conducted if needed. When tooth extraction was required following ineffective conservative treatment**,** preventive dental treatment was performed before extraction in all patients receiving BP, and extraction was conducted with particular care and antibiotic use, with complete wound closure when possible.

The estimated incidence of BIONJ associated with tooth extraction in the literature ranges from 8.3% to 40%[5, 15, 25]. The present study found a cumulative incidence of BIONJ after extraction at 42 months among all patients receiving BP and those receiving intravenous BP of 3.9% and 14.8%, respectively. Saia et al. reported that 5 of 60 patients receiving BP by either route developed BIONJ after tooth extraction (8.3%) within 12 months[25]. In a large cohort of 3994 patients with intravenous BP administration, Hoff et al. reported that 16 (10.5%) of 152 patients with tooth extraction developed BIONJ within 90 months, while in 1621 patients receiving intravenous BP[5], Vahtsevanos et al. reported that 46 of 115 patients with a history of tooth extraction

developed BIONJ (40%) within 106 months[15]. The results of our present study are consistent with these other studies which also employed positive preventive dental treatment before tooth extraction, and better than that of the study which did not describe the use of preventive care[15]. In addition, Mawardi et al. reported that bacterial infection at tooth extraction sites caused diminished keratinocyte growth factor expression in gingival fibroblasts, leading to a delay in the epithelial wound-healing process *in vitro* and *in vivo* experiments[26]. These results are consistent with the hypothesis that poor oral hygiene might be associated with an increased risk of BIONJ after tooth extraction. Preventive and therapeutic treatment of oral bacterial infection before extraction might be important in preventing BIONJ in patients with BP administration.

Periodontal disease, an infection caused by oral bacteria, is characterized by inflammation that leads to alveolar bone loss[27]. In this study, we found that not only intravenous BP administration but also the loss of alveolar bone was associated with an increased risk of BIONJ after tooth extraction. Given that all patients with BP administration underwent preventive and therapeutic treatment of oral bacteria before tooth extraction and that any effect of infection at the time of extraction was accordingly minimum, our findings suggest that previous inflammation of periodontal tissue may

predispose to BIONJ after tooth extraction.

Several limitations of this study warrant mention. First, large differences were seen in age and prevalence of cancer or osteoporosis between BP and BP-naïve patients. We therefore performed stratified analysis by age and route of BP administration to estimate risk ratios for ONJ to control for these factors. However, due to the limited number of events, we were unable to estimate relative risks adjusted for the other potential risk factors such as steroid use or smoking, and the 95% CIs were wide. This prevents the drawing of any reliable conclusions from the results, and indicates the need to evaluate possible risk factors or relative risks in a larger number of patients with ONJ, or to conduct a case-control study. Second, selection bias is inherent to single-center studies, and the present study was additionally subject to inherent referral bias toward the selection of more severe cases, given that our department is a lead institution for oral and maxillofacial surgery in Kyoto City. A positive aspect of this latter limitation, however, is that almost all patients consult our department again in the event of subsequent problems at the tooth extraction site. Additionally, ONJ is an uncommonly encountered clinical condition, and such patients are likely to be referred to our clinic to establish a diagnosis. The impact of selection bias is thus somewhat unclear. Subsequent multicenter regional (or national) studies would be required to address this bias. Third,

we were unable to eliminate the possibility that some of the patients who developed ONJ might have had unidentified ONJ in the submucosa at the time of tooth extraction, hampering assessment of the impact of tooth extraction on ONJ development. A comprehensive understanding of the mechanism of ONJ therefore awaits additional studies.

In conclusion, BP administration, particularly intravenous administration, is associated with an increased risk of ONJ after tooth extraction. Severe alveolar bone loss might be a risk factor for BIONJ after tooth extraction. This study provides important information for physicians and dentists concerned with the prevention of ONJ in patients receiving BP.

Competing interests

None declared.

Funding

None.

Ethical approval

This study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine.

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Tables

Table 1. Patient characteristics

Characteristic	BP administration	
	Yes (n = 126)	No (n = 3090)
Age, years		
Median	66.0	39.0
Range	26 - 88	20 - 94
Sex (%)		
Male	23 (18.3)	1490 (48.2)
Female	103 (81.7)	1600 (51.8)
Primary disease (%)		
Osteoporosis*	99 (78.6)	74 (2.4)
Breast cancer*	13 (10.3)	61 (2.0)
Multiple myeloma	11 (8.7)	5 (0.2)
Prostate cancer	1 (0.8)	41 (1.3)
Kidney cancer	3 (2.4)	1 (0.03)
Other cancer	6 (4.8)	184 (5.6)
Route of BP administration (%)		
Oral	99 (78.6)	*N.A.*
Intravenous	27 (21.4)	*N.A.*

BP = bisphosphonate; N.A. = not applicable

*Seven patients with BP administration were diagnosed with both osteoporosis and breast cancer.

Table 2. Demographic and clinical characteristics of ONJ patients

Sex	Age	Primary disease	Type of BP	Dosage of BP (mg)	Duration of BP (mon)	Other risk factors	Cure and prognosis
F	75	Osteoporosis	A	1990	13	None	Sequestrectomy, healing
F	75	Breast cancer	P Z	1455 16	45 4	Chemo therapy	Currettage, nonhealing
F	68	Multiple myeloma	P	1305	19	Thalidmide Steroid	Sequestrectomy, healing
M	75	Prostate cancer	Z	32	8	Chemo therapy	Die of primary disease
M	67	Kidney cancer	Z	28	7	None	Sequestrectomy, healing
M	73	None	None	-	-	None	Sequestrectomy, healing

ONJ = Osteonecrosis of the jaw; BP = bisphosphonate; A = alendronate; P = pamidronate; Z = zoledronic acid;

Table 3. Stratified analysis of osteonecrosis of the jaw after tooth extraction

	ONJ (+) (n=6)	ONJ (-) (n=3210)	Total (n=3216)	Risk ratio (95% CI)	*P* value
Total					
BP (+)	5 (83.3)	121 (3.8)	126	122.6 (14.4-1041.8)	< **0.001**
BP (-)	1 (16.7)	3089 (96.2)	3090	1.0 (ref)	
BP-stratified					
Oral BP (+)	1 (16.7)	98 (3.1)	99	31.2 (1.9-495.4)	0.061
IV BP (+)	4 (66.6)	23 (0.7)	27	457.7 (52.8-3962.7)	< **0.001**
BP (-)	1 (16.7)	3089 (96.2)	3090	1.0 (ref)	
Age-stratified (65 years >=)					
BP (+)	5 (16.7)	63 (8.3)	68	51.5 (6.1-434.8)	< **0.001**
BP (-)	1 (83.3)	700 (91.7)	701	1.0 (ref)	
Age-stratified (65 years <)					
BP (+)	0	58 (2.4)	58	*N.A*	*N.A*
BP (-)	0	2389 (97.6)	2389	1.0 (ref)	
BP- and age-stratified (65 years >=)					
Oral BP (+)	1 (16.7)	53 (7.0)	54	12.9 (0.82-204.6)	0.138
IV BP (+)	4 (66.6)	10 (1.3)	14	200.2 (23.8-1679.4)	< **0.001**
BP (-)	1 (16.7)	700 (91.7)	701	1.0 (ref)	
BP- and age-stratified (65 years <)					
Oral BP (+)	0	45 (1.8)	45	*N.A.*	*N.A.*
IV BP (+)	0	13 (0.53)	13	*N.A.*	*N.A.*
BP (-)	0	2389 (97.6)	2389	1.0 (ref)	

The Fisher exact test was used to compare differences in the incidence of osteonecrosis of the jaw between patients with and without BP administration.

Statistically significant *P* values appear in **bold**.

ONJ = Osteonecrosis of the jaw; CI = confidence interval; BP = bisphosphonate; IV = intravenous; ref = reference; N.A. = not applicable

Table 4. Potential risk factors for osteonecrosis of the jaw after tooth extraction

Variable	Bisphosphonate-induced osteonecrosis of the jaw			
	Yes (n = 5)	No (n = 121)	RR (95%CI)	*P* value
Sex - no. (%)				
Male	2 (40.0)	21 (17.4)	2.9 (0.52-16.8)	0.225
Female	3 (60.0)	100 (82.6)	1.0 (ref)	
Age				
Median	75.0	65.0	*N.A.*	0.133
Range	67-77	26-88		
Administration route - no. (%)				
Intravenous	4 (80.0)	23 (19.0)	14.6 (1.7-125.8)	**0.007**
Oral	1 (20.0)	98 (81.0)	1.0 (ref)	
Steroid use - no. (%)				
Yes	2 (40.0)	54 (44.6)	0.83 (0.14-4.8)	1.000
No	3 (60.0)	67 (55.4)	1.0 (ref)	
Chemotherapy use - no. (%)				
Yes	3 (60.0)	23 (19.0)	5.7 (1.0-32.7)	0.059
No	2 (40.0)	98 (81.0)	1.0 (ref)	
Diabetes - no. (%)				
Yes	0 (0)	9 (7.4)	*N.A.*	*N.A.*
No	5 (100)	112 (92.6)		
Current smoking - no. (%)*				
Yes	0 (0)	21 (18.4)	*N.A.*	*N.A.*
No	5 (100)	93 (81.6)		
Current alcohol intake - no. (%)*				
Yes	1 (20.0)	29 (25.4)	0.74 (0.086-6.3)	1.000
No	4 (80.0)	85 (74.6)	1.0 (ref)	
DMF count				
median	21	19	*N.A.*	0.548
range	13 - 28	0 - 28		
D count				
median	2	1	*N.A.*	0.085
range	1 - 4	0 - 15		
M count				
median	7	5	*N.A.*	0.209
range	6 - 14	0 - 27		

F count				
median	10	10	*N.A.*	0.910
range	4 - 14	0 - 25		
Bone loss score				
median	1.6	1.3	*N.A.*	**0.022**
range	1.5 - 2.2	1.0 - 3.5		

P values were calculated using the Fisher exact test or Wilcoxon rank-sum test.

The Fisher exact test was used to compare differences in the presence of potential risk factor between patients with and without BIONJ.

Statistically significant *P* values appear in **bold**.

RR = risk ratio; CI = confidence interval; ref = reference; N.A. = not applicable;

D = decayed teeth; M = missing teeth; F = filling teeth

* Data were not available for seven patients and the valid percentages are shown.

Table 5. Type, dosage and duration of intravenous BP administration

	Bisphosphonate-induced osteonecrosis of the jaw		
Dosage of IV BP administration (mg)			
	Yes (n = 4)	No (n = 22*)	
Single-drug administration			
Incadronate			
no.	0	1	
median (range)	0	40	
Pamidronate			
no.	1	2	
median (range)	1305	30 (15 - 45)	
Zoledronic acid			
no.	2	11	
median (range)	30 (28 - 32)	44 (4 - 104)	
Combined-drug administration			
Incadronate + Pamidronate			
no.	0	2	
median (range)	0	*I*: 1640 (210 - 3070) *P*: 1608 (470 - 2745)	
Pamidronate + Zoledronic acid			
no.	1	6	
median (range)	*P*: 1455 *Z*: 16	*P*: 75 (30 - 2160) *Z*: 50 (12 -56)	
Duration of IV BP administration (month)			
	Yes (n = 4)	No (n = 22*)	*P* value
median (range)	13.5 (7 - 49)	7.5 (1 - 96)	0.333

P values were calculated using the Wilcoxon rank-sum test.

* Data were not available for one patient.

BP = bisphosphonate; I = incadronate; P = pamidronate; Z = zoledronic acid;

IV = intravenous