

Nationwide Survey for Bisphosphonate-Related Osteonecrosis of the Jaws in Japan

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Purpose: A nationwide retrospective cohort study was conducted by the Japanese Society of Oral and Maxillofacial Surgeons to assess the occurrence of bisphosphonate (BP)-related osteonecrosis of the jaws (BRONJ) during 2006 to 2008 and to elucidate the outcome and factors associated with remission of BRONJ.

Materials and Methods: A written questionnaire, including the clinical characteristics, management, and outcome of patients with BRONJ, was sent to 248 institutions certified as training facilities by the Japanese Society of Oral and Maxillofacial Surgeons in 2008.

Results: A total of 568 patients with BRONJ, including suspicious cases, were registered. Of these 568 patients, 263, including the maxilla in 81, the mandible in 160, and both in 22, met the working definition of BRONJ proposed by the American Association of Oral and Maxillofacial Surgeons. The patients included 219 women (83.3%) and 44 men (16.7%). Of these patients, 152 (57.8%) had received intravenous BPs, 104 (39.5%) had received oral BPs, and 7 (2.7%) had received both. The mean duration of administration until onset of BRONJ was 23.6 months for intravenous BPs and 33.2 months for oral BPs. BRONJ was stage 1 in 42 patients (16.0%), stage 2 in 187 (71.1%), stage 3 in 32 (12.2%), and unknown in 2. Of these patients, 34.2% had remission of BRONJ, 46.0% had persistent or progressive disease, and 19.7% died of malignancy or were lost to follow-up. Statistical analysis revealed that surgical treatment, including tooth extraction, sequestrectomy, and segmental mandibulectomy, contributed to the remission of BRONJ. In contrast, conservative treatment, concurrent anticancer drugs, poor oral hygiene, and the use of intravenous BPs did not.

Conclusions: The relative ratio of BRONJ related to the use of oral BPs was greater in Japan than in the United States and European Union. Surgical treatment contributed to remission of BRONJ, and conservative treatment, concurrent anticancer drugs, poor oral hygiene, and intravenous BPs did not.

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Bisphosphonates (BPs) are very effective for the management of hypercalcemia of malignancy and skeletal events associated with multiple myeloma, bone metastases from breast cancer and prostate cancer, and osteoporosis. Despite various benefits, however, the development of BP-related osteonecrosis of the jaws (BRONJ) has become an increasingly serious problem in a subset of patients, especially those receiving intravenous preparations. The first cases of BRONJ were reported in 2003 in the United States.^{1,2} Subsequently, more than 2,500 similar cases were reported worldwide as of 2006.³ BRONJ has also developed in patients who received oral BPs, although the incidence is extremely low.^{4,5} Most cases of BRONJ occurred after dental procedures such as tooth extraction, periodontal surgery, and dental implant placement and have been refractory to conventional treatment, including debridement, antibiotics, and hyperbaric oxygen therapy. Compared with the United States and the European Union, the number of BRONJ cases has remained low in Japan but has been increasing annually. The first nationwide survey for the occurrence of BRONJ in Japan was performed at 239 institutions certified as training facilities by the Japanese Society of Oral and Maxillofacial Surgeons (JSOMS) in 2006.^{6,7} A total of 28 patients with BRONJ (3 men and 25 women) were registered. The mandible was involved in 23, the maxilla in 4, and both in 1. Of these 28 patients, 17 (60.7%) had received intravenous BPs, 9 (32.1%) had received oral BPs, and 2 had received both. Also, 22 patients had undergone dentoalveolar surgery, including tooth extraction, immediately before or during treatment with BPs. Six patients received no dental treatment. In addition to antibiotic therapy, surgical treatment such as sequestrectomy and curettage was performed. Of the 28 patients, 8 had complete remission, 17 continued to receive treatment, and 3 had progressive disease.

In a follow-up survey performed 2 years later, 9 additional patients were considered to have complete remission. Thus, 17 (60.7%) of the 28 patients had complete remission, but healing was delayed in 12 patients. Of the 17 patients, 9 (52.9%) had received intravenous BPs, and 7 (77.8%) of the 9 patients given oral BPs had complete remission. In that small case series, surgical treatment such as sequestrectomy, curettage, and resection of the jawbone was performed in a slightly greater proportion of patients with remission than in patients with persistent disease. In contrast, a greater proportion of patients with persistent disease had received conservative treatment compared with the patients with remission. These results suggested that surgical treatment performed at an appropriate time contributed to the remission of BRONJ and conservative treatment did not, even if disease progression was slow.⁷

Because the number of BRONJ cases rapidly increased after the first survey, we performed a second nationwide survey to assess the occurrence of BRONJ in 2008. In the present study, we report the present status and clinical characteristics of BRONJ in Japan and identify the factors associated with remission.

Materials and Methods

This second nationwide survey of BRONJ was performed in 2008 by the Committee of Survey and Planning of the JSOMS as retrospective cohort study. Detailed information on the patients with these diagnoses was obtained by written questionnaires sent by the JSOMS to 248 institutions in June 2008. These institutions included university hospitals and major municipal or private hospitals having an oral and maxillofacial surgery department. Data were collected on gender and age, clinical symptoms, radiographic findings, history of radiotherapy to the jaws, concurrent use of anticancer drugs and corticosteroids, oral hygiene, medical comorbidities such as diabetes mellitus, obesity (body mass index >25), and malnutrition (anemia, hemoglobin <9.0 g/dL; low proteinemia, total protein <5.0 g/dL, albumin <2.5 g/dL), indications and type of BPs, duration of BP administration, triggering events, treatments, and outcomes.

Cases of BRONJ satisfying the working definition of the American Association of Oral and Maxillofacial Surgeons (AAOMS)⁸ (including exposed necrotic bone persisting for >8 weeks and no history of radiotherapy to the jaws) that developed in patients in whom the type of BP, duration of administration, and outcomes could be tracked from the clinical records were evaluated as confirmed cases of BRONJ. Those with insufficient information were excluded from the study. In addition, the stage of BRONJ was determined by the AAOMS staging classification of 2007⁸; thus, the questionnaires for the present survey did not include stage 0.

Statistical analysis was performed using the χ^2 test or Fisher exact test to examine the relationship between background or treatment of the patients and outcomes. Stage and oral hygiene were subdivided into 3 categories (stage 1 and common oral hygiene were set as the reference), the logistic regression analysis was performed using the outcome as an objective variable, and the odds ratio and 95% confidence intervals (CIs) were calculated. In addition, the Cox proportional hazard model was performed using the outcome as an objective variable, BP administration period as a survival variable, and the factors that in the χ^2 test or Fisher exact test was less than 5% as covariate and the hazard ratio (HR) and 95% CI were calculated. Thus, persistent or progressive disease,

death from malignancy, and loss to follow-up were set at “0,” remission was set at “1,” no was set at “0,” and yes was set at “1” for the background factors or treatment. Sheets with no answer were excluded from the subject for analysis. Throughout the analysis, a level of 5% was used to denote statistical significance. All the calculations were performed using the Statistical Package for Social Sciences, version 15.0, statistical software (SPSS, Chicago, IL).

Results

Of the 248 institutions sent questionnaires, 188 (75.8%) responded, and 160 (85.1% of the 188) reported cases of BP-related osteomyelitis and osteonecrosis of the jaws. A total of 568 cases of BRONJ, including suspicious cases, were registered. Of these cases, 263 satisfied the diagnostic criteria described in the “Materials and Methods” section and were evaluated as confirmed cases of BRONJ. The remaining 305 cases with insufficient information were considered unsuitable for analysis. The patients with confirmed BRONJ included 44 men (16.7%) and 219 women (83.3%), with a mean age of 68.1 years (range 36 to 88; Table 1).

BP INDICATIONS AND TYPES

Of the 263 patients with confirmed BRONJ, 57.8% had received intravenous BPs and 39.5% had received oral BPs, indicating a greater proportion of cases related to oral BPs in Japan than in the United States and the European Union. These BPs were frequently used to treat multiple myeloma, bone metastasis from breast cancer, and osteoporosis. Regarding the specific preparations used, pamidronate and zoledronic acid were the main intravenous BPs and alendronate and risedronate the main oral BPs. Two thirds of the patients received 1 type of BPs and the remaining received more than 2 types. The mean duration of administration until the onset of BRONJ was 23.6 months for intravenous BPs and 33.2 months for oral BPs (Table 1). The duration of each BP was 20.5 months for pamidronate (n = 12), 11.8 months for zoledronic acid (n = 52), 26.8 months for pamidronate later changed to zoledronic acid (n = 56), 33.6 months for alendronate (n = 58), and 31.6 months for risedronate (n = 27).

INITIAL SYMPTOMS AND CLINICAL MANIFESTATIONS

The initial signs and symptoms of BRONJ were bone exposure in 154 patients (48.7%), swelling in 50 (15.8%), pain in 49 (15.5%), pus discharge in 33 (10.4%), tooth loss in 11, intraoral fistula in 10, poor healing of a tooth extraction socket in 9, tooth loosening in 4, bleeding in 4, redness in 3, mental pares-

Table 1. PATIENT CHARACTERISTICS

Characteristic	Value
Age (yr)	
Mean	68.1
Range	36–88
Gender	
Men	44 (16.7)
Women	219 (83.3)
Bone disease	
Multiple myeloma	36 (13.7)
Bone metastasis from breast cancer	104 (39.5)
Bone metastasis from prostate cancer	9 (3.4)
Other bone metastasis	14 (5.3)
Osteoporosis	100 (38.0)
BP type	
Intravenous	152 (57.8)
Oral	104 (39.5)
Both	7 (2.7)
Bisphosphonate preparations	
Pamidronate	102 (25.7)
Zoledronic acid	144 (36.3)
Incadronate	24 (6.0)
Alendronate	1 (0.3)
Oral alendronate	79 (19.9)
Risedronate	42 (10.6)
Etidronate	5 (1.3)
BP types administered (n)	
1	162 (61.6%)
2	73 (27.8%)
3	23 (8.7%)
4	5 (1.9%)
Affected jaw	
Mandible	160 (60.8)
Maxilla	81 (30.8)
Both	22 (8.4)
BRONJ stage	
Stage 1	42 (16.0)
Stage 2	187 (71.1)
Stage 3	32 (12.2)
Unknown	2 (0.8)
Treatment duration until onset (mo)	
Intravenous BP	
Mean	23.6
Range	1.2–103.0
Oral BP	
Mean	33.2
Range	0.2–135.1
Both	
Mean	38.6
Range	11.0–87.4
Concurrent medication	
No	55 (20.9)
Anticancer drugs	72 (27.4)
Corticosteroids	46 (19.5)
Both	53 (20.1)
Unknown	37 (14.1)
Smoking/alcohol use	
No	185 (70.3)
Smoking	15 (5.7)
Alcohol use	18 (6.8)
Both	17 (6.8)
Unknown	28 (10.6)

Table 1. (Cont'd)

Characteristic	Value
Systemic factors	
Anemia	71 (27.0)
Low proteinemia	44 (16.7)
Diabetes mellitus	42 (16.0)
Obesity (body mass index >25)	33 (12.5)
Unknown	73 (27.7)
Oral hygiene	
Good	31 (11.8)
Common	169 (64.3)
Poor	58 (22.1)
Unknown	5 (1.9)
Triggering events	
Tooth extraction	108 (41.1)
Curettag	2 (0.8)
Dental implants	1 (0.4)
Biopsy	1 (0.4)
Unknown	151 (57.4)

Abbreviations: BRONJ, bisphosphonate-related osteonecrosis of the jaws; BP, bisphosphonate; AAOMS, American Association of Oral and Maxillofacial Surgeons.

Stage of BRONJ determined using AAOMS staging classification,⁸ in which stage 0 was not included.

Data presented as numbers, with percentages in parentheses, unless otherwise noted.

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thesia in 2, an uncomfortable feeling in 2, and jaw fracture in 1. Some patients had more than 1 initial sign or symptom. The mandible was involved in 160 patients (60.8%), the maxilla in 81 (30.8%), and both jaws in 22 (8.4%).

The most common clinical manifestations of BRONJ, except for bone exposure, were pain in 291 patients (33.9%), pus discharge in 167 (22.9%), swelling in 148 (17.2%), intraoral fistula in 69, tooth loosening in 63, fatigue in 61, mental paresthesia in 35, and fever in 25. Most of the patients had more than 1 initial symptom and clinical manifestation.

RADIOGRAPHIC FINDINGS

The radiographic examinations, including panoramic radiography, computed tomography, and magnetic resonance imaging, revealed sequestration in 139 patients (32.2%), osteolysis in 112 (25.9%), osteosclerosis in 104 (24.1%), sclerosis of the lamina dura or cortical bone thickening of the alveolar ridge in 40, widening of the periodontal ligament space in 23, and no particular findings in 14. Some patients had more than 1 type of radiographic finding.

CONCURRENT MEDICATION AND MEDICAL COMORBIDITIES

Of the 263 patients with confirmed BRONJ, 75.7%, excluding those with unknown data, received anti-cancer drugs and/or corticosteroids. Approximately

40% of the patients with BRONJ related to oral BPs and 45% of those with BRONJ related to intravenous BPs had received corticosteroids. Approximately 9% of patients with BRONJ related to oral BPs and 81% of those with BRONJ related to intravenous BPs received anticancer drugs. A history of smoking and alcohol use were found in 19.3%, and systemic factors such as anemia, proteinemia, diabetes mellitus, and obesity were observed in 27.0%, 16.7%, 16.0% and 12.5%, respectively. Poor oral hygiene was seen in 22.1% of the patients.

TRIGGERING EVENTS

The most suspected causative event was tooth extraction occupying 41.1% of the patients, and curettag, dental implant placement, and biopsy was few. The apparent triggering event was unknown in 57.4%.

BRONJ STAGE

According to the AAOMS staging classification,⁸ approximately 70% of the BRONJ cases were stage 2, followed by stage 1 in 16.0% and stage 3 in 12.2%. No difference was found in the distribution of BRONJ according to stage between those who had received intravenous BPs and those who had received oral BPs. In patients who received intravenous BPs and those who received oral BPs, the stage of BRONJ was stage 1 in 28 (18.4%) and 14 (13.5%), stage 2 in 104 (68.4%) and 76 (73.1%), and stage 3 in 19 (12.5%) and 13 (12.5%) patients, respectively.

TREATMENTS AND OUTCOMES

Various treatments, such as conservative and surgical treatment, including antibiotics, discontinuation of BP administration, and hyperbaric oxygen therapy, resulted in remission of BRONJ in 34.2% of the patients. However, 46.0% of the patients had persistent or progressive disease. Of the patients with remission, 42% showed delayed healing extending up to 2 years (Table 2). Surgical treatment such as tooth extraction ($P = .03$, HR 1.75, 95% CI 1.04 to 2.92), sequestrectomy ($P < .01$, HR 3.12, 95% CI 1.88 to 5.18), and segmental mandibulectomy ($P < .01$, HR 10.99, 95% CI 3.80 to 31.8) contributed significantly to the remission. In contrast, conservative treatment such as irrigation and scaling did not contribute to the remission significantly ($P < .01$, HR 0.40, 95% CI 0.26 to 0.62; Table 3). No significant contribution was found for the outcomes in the discontinuation of BPs, administration of antibiotics, or hyperbaric oxygen therapy. The rate of remission was greater for the patients with BRONJ related to oral BPs than for those with BRONJ related to intravenous BPs (Table 4) and slightly greater for patients with early-stage BRONJ than for those with late-stage BRONJ (Table 5). In addition,

Table 2. TREATMENT OUTCOMES OF BRONJ

Outcome	Patients (n)
Remission (easy)	52 (19.8)
Remission (delayed)	38 (14.4)
Persistent disease	97 (36.9)
Progressive disease	24 (9.1)
Death due to malignancy	24 (9.1)
Lost to follow-up	28 (10.6)

Abbreviation: BRONJ, bisphosphonate-related osteonecrosis of the jaws.

Data in parentheses are percentages.

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poor oral hygiene significantly affected the remission. Anticancer drugs also tended to affect remission (Table 4). However, corticosteroids, smoking/alcohol use, anemia, low proteinemia, diabetes mellitus, and obesity did not affect remission in the present survey (Tables 4, 5).

Discussion

BRONJ was first reported as a serious side effect of long-term BP treatment by Marx¹ and Migliorati² in the United States in 2003. Most of the 36 cases reported by Marx¹ and the 5 cases reported by Migliorati² were related to the use of intravenous BPs to treat hypercalcemia in patients with multiple myeloma and metastatic breast cancer. After these initial reports, the number of reported cases of BRONJ rapidly increased worldwide. In Japan, the first case of BRONJ was documented in 2006. It involved the maxilla of an 81-year-old woman with bone metastasis from breast cancer who had received chemotherapy and pamidronate.⁹ In the first nationwide survey in

Japan in 2006, 28 cases were evaluated to be confirmed cases of BRONJ, and 60.7% of the patients had received intravenous BPs and 32.1% had received oral BPs. In other countries, such as the United States, the European Union, and Australia, approximately 95% of all cases of BRONJ were related to intravenous BPs, and only about 5% were related to oral BPs.^{4,5,10,11} Thus, the relative proportion of oral BP-related BRONJ was apparently greater in Japan than in other countries.

In the present survey, conducted in 2008, the response rate of institutions to the questionnaire was high (75.8%), indicating increasing awareness of interest in BRONJ. From these institutions, 568 cases of BRONJ, including suspicious ones, were registered. Because many questionnaires were incomplete, requests for additional information were sent to the relevant institutions to obtain the missing data. Cases with missing data for the BP type, treatment duration, or outcomes were excluded from the analysis. A total of 263 cases that met the AAOMS working definition of BRONJ were evaluated. Similar to the results of the first survey, the relative proportion of oral BP-related cases was greater (39.5%) in Japan than in Europe and North America. The greater proportion of oral BP-related cases might have been related to differences between Japan and the United States and Europe in the approval times and the number of prescriptions issued for intravenous (pamidronate, zoledronic acid) and oral BPs (alendronate, risedronate). In addition, oral hygiene among the elderly might be poorer in Japan than in other developed countries. Intravenous BPs were approved relatively recently for the indication of bone metastasis from breast cancer and multiple myeloma in Japan compared with the United Kingdom and the United States. In contrast, oral BPs

Table 3. STATISTICAL ANALYSIS RESULTS BETWEEN TREATMENT AND OUTCOME

Treatment	χ^2 Test or Fisher Exact Test			Cox Proportional Hazards Model		
	Persistent (n = 173)	Remission (n = 90)	P Value	HR	95% CI	P Value
Discontinuation of BP	141 (81.5)	77 (85.6)	.41	0.40	0.26-0.62	<.01
Conservative treatment	137 (79.2)	43 (47.8)	<.01			
Antibiotics	161 (93.1)	78 (86.7)	.09	1.75	1.04-2.92	.03
Hyperbaric oxygen	13 (7.5)	9 (10.0)	.49			
Treatment tooth extraction	20 (11.6)	19 (21.1)	.04	3.12	1.88-5.18	<.01
Curettage	51 (29.5)	33 (36.7)	.24			
Sequestrectomy	68 (39.3)	68 (75.6)	<.01	10.99	3.80-31.8	<.01
Marginal mandibulectomy	3 (1.7)	2 (2.2)	.56			
Segmental mandibulectomy	0 (0)	4 (4.4)	.01			

Abbreviations: BP, bisphosphonate; HR, hazard ratio; CI, confidence interval.

Data in parentheses are percentages.

Statistical analysis performed using χ^2 test or Fisher exact test and Cox proportional hazards model (see "Materials and Methods" section for details).

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Table 4. STATISTICAL ANALYSIS RESULTS BETWEEN PATIENT CHARACTERISTICS AND OUTCOME

Characteristic	χ^2 Test or Fisher Exact Test			Cox Proportional Hazards Model		
	Persistent (n = 173)	Remission (n = 90)	P Value	HR	95% CI	P Value
Anticancer drugs	94 (60.3)	31 (44.3)	.03	1.29	0.59-2.78	.52
Corticosteroids	66 (42.3)	33 (47.1)	.50			
Anemia	48 (27.7)	23 (25.6)	.70			
Low proteinemia	33 (19.1)	11 (12.2)	.16			
Diabetes mellitus	23 (13.3)	19 (21.1)	.10			
Obesity (BMI>25)	19 (15.1)	14 (17.7)	.62			
Smoking	18 (11.6)	14 (16.3)	.31			
Alcohol	25 (16.3)	10 (12.3)	.42			
Intravenous BP	121 (69.9)	38 (42.2)	<.01	0.47	0.11-2.10	.32
Oral BP	57 (32.9)	54 (60.0)	<.01	1.57	0.37-6.70	.54
Maxilla	64 (37.0)	39 (43.3)	.32			
Mandible	122 (70.5)	58 (64.4)	.31			

Abbreviations: BMI, body mass index; other abbreviations as in Table 3.

Data in parentheses are percentages that each patient number occupies in patients with persistent disease or remission, with the maximum of 173 and 90, respectively, because of including patients with “no” and “unknown.”

Statistical analysis performed using χ^2 test or Fisher exact test and Cox proportional hazards model (see “Materials and Methods” section for details).

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were approved for the treatment of osteoporosis at about the same time in Japan and the European Union. Also, another reason might be that the prevalence of osteoporotic fracture is greater in Japanese women than in white women older than 50 years.¹² This is thought to result from factors such as small stature, low dietary calcium, a low level of activity, and the high rate of lactose intolerance in the Japanese compared with whites. Because approximately 1 million patients with osteoporosis receive oral BPs in Japan, the incidence of BRONJ related to oral BP preparations is speculated to be 0.01% to 0.02%.¹³ Recent studies have suggested that the relative frequency of BRONJ in patients with osteoporosis is

greater than previously thought. Sedghizadeh et al¹⁴ reported that 9 (4%) of 208 patients with a history of alendronate use had active BRONJ in a large institutional study in United States. Lazarovici et al¹⁵ found that 16 (16%) of 101 cases of BRONJ were associated with oral BP use in a single-center study in Israel, and Otto et al¹⁶ reported that 37 (7.8%) of 470 cases of BRONJ were associated with oral BPs in a multicenter study in Europe. Although not as high a rate as in these studies, Lo et al¹⁷ reported a prevalence of 0.10% in 8,572 survey responders receiving chronic oral BP therapy. Additional studies are needed to confirm the relation between oral BP use and BRONJ.

Table 5. STATISTICAL ANALYSIS RESULTS BETWEEN STAGE OR ORAL HYGIENE AND OUTCOME

Variable	Logistic Regression Analysis				Cox Proportional Hazards Model			
	Persistent (n = 173)	Remission (n = 90)	OR	95% CI	P Value	HR	95% CI	P Value
Stage								
1	24 (14.0)	18 (20.0)	Reference		<.01			.13
2	123 (71.9)	64 (71.1)	0.52	0.38-0.70	<.01	0.63	0.37-1.08	.09
3	24 (14.0)	8 (8.9)	0.33	0.15-0.74	.01	0.46	0.20-1.07	.07
Oral hygiene								
Common	104 (61.2)	65 (73.9)	Reference		<.01			.04
Good	20 (11.8)	11 (12.5)	0.55	0.26-1.15	.11	0.90	0.47-1.73	.76
Poor	46 (27.1)	12 (13.6)	0.26	0.14-0.49	<.01	0.40	0.23-0.83	.01

Abbreviations as in Table 3.

Data in parentheses are percentages that each patient number occupies in patients with persistent disease or remission, with the maximum of 173 and 90, respectively, because of including patients with “no” and “unknown.”

Statistical analysis performed using logistic regression analysis and Cox proportional hazards model (see “Materials and Methods” section for details).

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The affected jaws, duration of BP administration until onset of BRONJ, initial signs and symptoms, clinical manifestations, and radiographic findings in our survey were consistent with those in former studies.^{4,11} The concurrent use of anticancer drugs tended to be associated with the treatment outcome of BRONJ, but corticosteroid use was not. Wessel et al¹⁸ reported that zoledronate, smoking, and obesity are high-risk factors for BRONJ. Khamaisi et al¹⁹ proposed that diabetes mellitus also increases the risk of BRONJ. In our survey, zoledronic acid was the most frequently used intravenous BP, followed by pamidronate. Because zoledronic acid has almost completely replaced pamidronate in recent years in Japan, owing to its potent clinical effect on malignant bone disease, it is speculated that the occurrence of BRONJ will increase further. Poor oral hygiene also significantly affected the remission of BRONJ, although smoking, alcohol use, diabetes mellitus, and obesity did not. BRONJ frequently occurs after dentoalveolar surgery, including procedures such as tooth extraction, periodontal surgery, and dental implant placement.⁴ In our survey, the triggering event of BRONJ was tooth extraction in 41% of cases but unknown in 57%, suggesting these latter cases included a considerable number of BRONJ cases that developed spontaneously or from ill-fitting dentures. Dental implantation was involved in only 1 case.

The absolute incidence of BRONJ remains unclear, but the incidence of BRONJ associated with intravenous BPs is more than 100-fold greater than that associated with oral BPs.^{4,8} A previous study reported that stage 3 BRONJ, the most severe stage according to the AAOMS classification,⁸ occurs most commonly in patients given intravenous BP therapy. In contrast, BRONJ rarely progresses beyond stage 2 in patients receiving oral BPs.²⁰ In the present survey, however, the distribution of BRONJ according to stage did not differ between those receiving intravenous BPs and oral BPs. It is unknown whether the sensitivity to BPs differs between Japanese patients and patients in other countries.

Many practical guidelines for the prevention, diagnosis, and treatment of BRONJ have been proposed by investigators in the United States and Canada.²¹⁻²⁴ However, effective therapy for BRONJ remains to be defined. The importance of oral hygiene, patient education, and treatment (ie, conservative treatment) best suited for the clinical stage of BRONJ has been emphasized. Several investigators have reported that curettage or surgical resection of the jawbone, including procedures such as marginal and segmental mandibulectomy, as well as antibacterial therapy, can lead to the long-term resolution of the symptoms and remission of BRONJ, particularly in patients with stage 3 disease.^{10,25-27} In the present survey, surgical ther-

apy contributed to the remission of BRONJ. Surgery, however, could increase the risk of additional exposed and necrotic bones and thereby induce disease progression. As for the discontinuation of BP administration, some investigators have reported that the withdrawal of treatment effectively promotes the alleviation of symptoms or the healing of BRONJ, not only in patients receiving oral BPs,²⁴ but also in those receiving intravenous BPs.^{28,29} In our survey, however, discontinuation of BP administration did not significantly contribute to the remission of BRONJ. Therefore, additional clinical studies are needed to solve the problems related to the quality of life of patients, such as whether to perform conservative or surgical treatment and whether to continue or discontinue BP administration.

Finally, this survey indicated the need for greater awareness of the potential risk of BRONJ, even in patients who receive oral BPs. Our results suggest that closer cooperation with physicians prescribing BPs is essential. Patients should be instructed to maintain proper oral hygiene and to routinely undergo oral examinations to prevent BRONJ. Our findings have confirmed again that many cases of BRONJ are refractory to treatment.

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References

1. Marx RE: Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *J Oral Maxillofac Surg* 61:1115, 2003
2. Migliorati CA: Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 21:4253, 2003
3. Kuehn BM: Reports of adverse events from bone drugs prompt caution. *JAMA* 295:2833, 2006
4. Marx RE, Sawatari Y, Fortin M, Broumand V: Bisphosphonate-induced exposed bone (osteonecrosis/osteoporosis) of the jaws: Risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 63:1567, 2005
5. Woo SB, Hellstein JW, Kalmar JR: Systemic review: Bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 144:753, 2006
6. Shimahara M, Ariyoshi Y, Imai Y, et al: A survey of bisphosphonate-related osteomyelitis/osteonecrosis of the jaws (in Japanese with English abstract). *Jpn J Oral Maxillofac Surg* 53:594, 2007
7. Urade M, Tanaka N, Shimada J, et al: A follow-up survey of 30 cases of bisphosphonate-related osteomyelitis/osteonecrosis of the jaws: Present status after 2 years (in Japanese with English abstract). *Jpn J Oral Maxillofac Surg* 55:553, 2009
8. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 65:369, 2007
9. Takahashi K, Kawabata A, Koike H, et al: A case of osteonecrosis of the maxilla associated with the use of a bisphosphonate (in Japanese with English abstract). *Jpn J Oral Maxillofac Surg* 52:416, 2006

10. Abu-Id MH, Warnke PH, Gottschalk J, et al: "Bis-phosy jaws"-high and low-risk factors for bisphosphonate-induced osteonecrosis of the jaw. *J Craniomaxillofac Surg* 36:95, 2008
11. Mavrokokki T, Cheng A, Stein B, et al: Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. *J Oral Maxillofac Surg* 65:415, 2007
12. Ross PD, Fujiwara S, Huang C, et al: Vertebral fracture prevalence in women in Hiroshima compared to Caucasians or Japanese in the US. *Int J Epidemiol* 24:1171, 1995
13. Yoneda T, Hagino H, Sugimoto T, et al: Bisphosphonate-related osteonecrosis of the jaw: Position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan, Osteoporosis Society; Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology and Japanese Society of Oral and Maxillofacial Surgeons. *J Bone Miner Metab* 28:365, 2010
14. Sedghizadeh PP, Stanley K, Caligiuri M, et al: Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw: An institutional inquiry. *J Am Dent Assoc* 140:61, 2009
15. Lazarovici TS, Yahalom R, Taicher S, et al: Bisphosphonate-related osteonecrosis of the jaw: A single-center study of 101 patients. *J Oral Maxillofac Surg* 67:850, 2009
16. Otto S, Abu-Id MH, Fedele S, et al: Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: Not just a sporadic coincidence—A multi-centre study. *J Craniomaxillofac Surg* Epub 2010 Jun 25
17. Lo JC, O'Ryan FS, Gordon NP, et al: Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. *J Oral Maxillofac Surg* 68:243, 2010
18. Wessel JH, Dodson TB, Zavras AI: Zoledronate, smoking, and obesity are strong risk factors for osteonecrosis of the jaw: A case-control study. *J Oral Maxillofac Surg* 66:625, 2008
19. Khamaisi M, Regev E, Yarom N, et al: Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. *J Clin Endocrinol Metab* 82:1172, 2007
20. Assael LA: Oral bisphosphonates as a cause of bisphosphonate-related osteonecrosis of the jaws: Clinical findings, assessment of risks, and preventive strategies. *J Oral Maxillofac Surg* 67(5 Suppl.):35, 2009
21. Khosla S, Burr D, Cauley J, et al: Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 22:1479, 2007
22. Khan AA, Sandor GK, Dore E, et al: Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaws. *J Rheumatol* 35:1392, 2008
23. Edwards BJ, Hellstein JW, Jacobsen PL, et al: Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: An advisory statement from the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc* 139:1674, 2008
24. Ruggiero SL, Dodson TB, Assael LA, et al: American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. *J Oral Maxillofac Surg* 67:2, 2009
25. Carlson ER, Basile JD: The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 67(5 Suppl.):85, 2009
26. Engroff SL, Kim DD: Treating bisphosphonate osteonecrosis of the jaws: Is there a role for resection and vascularized reconstruction? *J Oral Maxillofac Surg* 65:2374, 2007
27. Nocini PF, Saia G, Bettini G, et al: Vascularized fibula flap reconstruction of the mandible in bisphosphonate-related osteonecrosis. *Eur J Surg Oncol* 35:373, 2009
28. Magopoulos C, Karakinaris G, Telioudis Z, et al: Osteonecrosis of the jaws due to bisphosphonate use: A review of 60 cases and treatment proposals. *Am J Otolaryngol* 28:158, 2007
29. Van den Wyngaert T, Claeys T, Huizing MT, Vermorcken JB, Fossion E: Initial experience with conservative treatment in cancer patients with osteonecrosis of the jaw (ONJ) and predictors of outcome. *Ann Oncol* 20:331, 2009