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ORIGINAL ARTICLE

Characteristics of the early stages of intravenous bisphosphonate-related osteonecrosis of the jaw in patients with breast cancer

AKIRA MATSUO [1], HAYATO HAMADA[1], HIROSHI KAISE[2], DAICHI CHIKAZU[1], KIMITO YAMADA[2] & NORIO KOHNO[2]

[1]*Department of Oral and Maxillofacial Surgery, and* [2]*Department of Breast Oncology, Tokyo Medical University, Shinjuku-ku, Tokyo, Japan*

Abstract

Objective. The clinical features of the early stages of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in patients with breast cancer remain unclear. A retrospective cohort study was conducted of patients with breast cancer who received intravenous bisphosphonate (BP) treatment in a single center in order to clarify the status of the early stages of BRONJ. ***Materials and methods.*** A BRONJ oral monitoring program was established in 247 breast cancer patients given intravenous BP treatment at the institution. The differences in age, BP treatment period, number of remaining teeth, oral hygiene status, presence of regular oral monitoring and the existence of suspected BRONJ (stage 0) among eight BRONJ and 36 non-BRONJ subjects who completed oral examinations were then compared. ***Results.*** BRONJ was observed in 0.4% of subjects on the first visit to the oral surgery clinic and in 3.2% of subjects during the follow-up period. Logistic regression analysis revealed that the odds ratio for identifying patients with BRONJ during follow-up by the presence of stage 0 at first visit was 24.0 (95% confidence interval [CI] = 3.6–161.7). The area under the receiver operating characteristic curve for identifying subjects with BRONJ by the presence of stage 0 was 0.82 (95% CI = 0.63–1.00). ***Conclusion.*** The results suggest that patients with stage 0 BRONJ on the first visit may progress to advanced BRONJ during the follow-up period. The oral monitoring program may contribute to the early detection of BRONJ.

Key Words: *bisphosphonate, osteonecrosis, breast cancer, oral hygiene*

Introduction

Bisphosphonates (BPs) are widely used to prevent skeletal-related events in patients with various diseases, especially osteoporosis [1] and solid cancers with bone metastasis [2]. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) has been widely recognized as a severe adverse reaction to BPs due to its unresponsiveness to treatment [3–7]. Therefore, the prevention and early detection of BRONJ should receive priority [8]. However, the exact conditions of the early stages of BRONJ remain unclear [9]. The American Association of Oral and Maxillofacial Surgery (AAOMS) classifies this disease into four stages and states that bone exposure for 8 months is evidence of BRONJ [3]. Recently, however, the staging has been updated and the concept of stage 0 (suspected BRONJ with no bone exposure) [10] was added. However, it is unknown whether patients with stage 0 may subsequently progress to advanced BRONJ. Consistent oral examinations for all intravenous BP treatment patients may be useful to clarify this problem. However, it is not possible for all these patients to be examined both on the first visit and during follow-up by experienced clinicians [11], especially in a large cohort. In our institution, an oral monitoring program of BRONJ incidence for all patients with breast cancer who receive intravenous BP treatment is in place, as a collaborative program among breast oncologists and oral and maxillofacial surgeons.

In the present study, we retrospectively evaluated the status of the early stages of BRONJ in breast cancer patients participating in this monitoring program and who were treated with intravenous BPs at a single center and set out to determine whether patients with stage 0 may subsequently progress to advanced BRONJ.

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Materials and methods

Patients

The Ethics Committee of our institution approved the research protocol of this study (No. 1570). A total of 274 breast cancer patients were administered intravenous BPs for multiple bone metastases at our institution between 2002–2009. We initiated an early oral monitoring program of BRONJ incidence for these patients from November 2005. A total of 247 patients were eligible for this study; 27 patients were excluded because they had died or were otherwise lost to follow-up until November 2005. These patients had been given 4 mg of zoledronic acid, 45 mg of pamidronate or 10 mg of ibandronic acid intravenously every 4 weeks. All eligible patients were Japanese and no patients had metastasis or had received previous irradiation to the jaw bone.

The methods of the oral monitoring program were as follows (Figure 1). First, breast oncologists informed the patient about BRONJ. Second, a medical interview regarding the patient's oral and maxillofacial conditions was conducted by the breast oncologist. Third, breast oncologists performed an oral examination, including the dentition, if possible. Patients were referred to the Department of Oral and Maxillofacial surgery if they fulfilled the following criteria: (1) they wished to participate and (2) an intra-oral or jaw bone problem was suspected. Comprehensive intra-oral examinations were then performed by a qualified oral and maxillofacial surgeon (A.M.), while panoramic radiographs were examined and oral hygiene instructions relayed to patients by an experienced oral hygienist. Subsequently, further detailed examinations of suspected BRONJ patients were performed and suitable treatments administered. Patients with risk factors for BRONJ, such as chronic periodontitis and stump teeth, were treated conventionally and surgical treatments were avoided if possible. Routine oral examinations were performed as frequently as possible, such as twice a week over a period of 6 months, depending on the dental conditions. For non-participants or would-be participants whose physical condition or other personal reasons made it difficult for them to also visit the Department of Oral and Maxillofacial Surgery, breast oncologists continued the medical interview in their routine medical examination for as long as possible. Patients then re-visited the Department of Oral and Maxillofacial Surgery when a breast oncologist recognized the necessity of further oral examination.

Clinical evaluations

The clinical data regarding the primary disease of all 247 subject patients from 2002 until June 2010 were retrospectively extracted from the patient medical clinic files. The clinical data regarding the oral and maxillofacial status from November 2005, when oral examinations were started, to June 2010 were retrospectively extracted from the patient dental clinic files.

The patients who visited the Department of Oral and Maxillofacial Surgery ($n = 44$) were divided into two groups, namely eight BRONJ and 36 non-BRONJ subjects. Diagnoses of BRONJ were based on the AAOMS criteria [3]. Suspected BRONJ patients who had some oral symptoms but no bone exposure were also classified as stage 0 in accordance with the updated version of the AAOMS criteria of

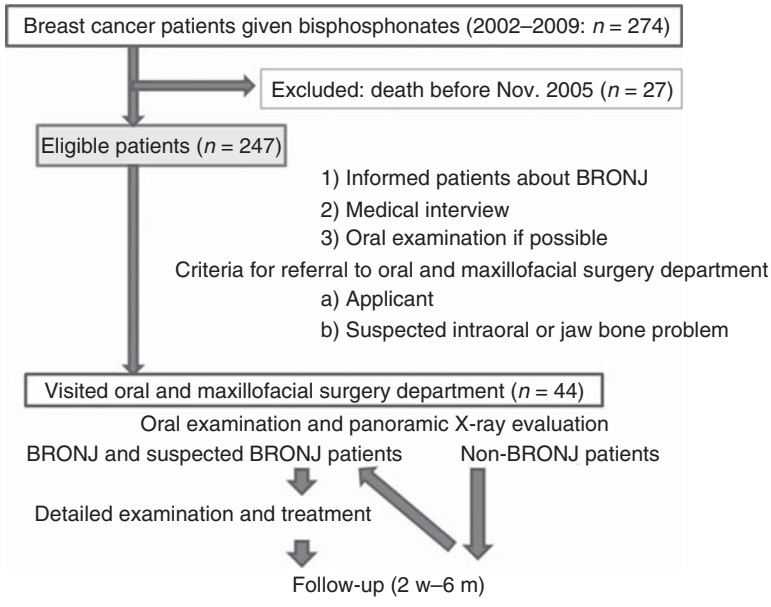

Figure 1. Schedule of our oral monitoring program for intravenous bisphosphonate-related osteonecrosis of the jaw in patients with breast cancer.

2009 [10]. Age, BP treatment period, type of BPs, performance status in accordance with the criteria of the Eastern Cooperative Oncology Group (ECOG) [11,12] and blood total protein were designated as systemic risk factors. At the first visit, the number of remaining teeth, oral hygiene and BP treatment duration before the first oral examination were designated as local risk factors. During subsequent follow-up, the presence of regular oral monitoring and the presence of stage 0 were compared between the BRONJ and non-BRONJ groups. The types of BP used were classified into the following three groups: zoledronic acid only (zoledronate group), pamidronate or ibandronic acid followed by zoledronic acid (zoledronate and other BPs group) and pamidronate or ibandronic acid only (other BPs group). Oral hygiene was classified into three categories (good, fair, poor) based on the consensus of one dentist and one dental hygienist. Patients who required regular oral monitoring had to fulfil three requirements. First, oral monitoring had been started within 6 months after initiating BP treatment. Second, an oral examination had been performed before the detection of BRONJ. Third, no period of treatment interruption of over 6 months during the follow-up period was recognized. This requirement was decided based on the fact that sporadic BRONJ cases have been reported after just a single BP dose and the majority of these were reported after more than 6 months of BP treatment [13].

Statistical analysis

All continuous variables were presented as means (±standard deviation). These variables were compared between the BRONJ and non-BRONJ groups. The unpaired *t*-test was used for analysis of the continuous variables and the chi-squared test was used for categorical variables.

Age, BP treatment period, number of remaining teeth, oral hygiene level, the presence of regular oral monitoring and the presence of stage 0 were selected as independent variables. The odds ratio [OR] (95% confidence internal [CI]) for identifying subjects with BRONJ by the presence of stage 0 after adjustment for possible risk factors was calculated by logistic regression analysis in a forward manner. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated to predict the presence of stage 0 BRONJ. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy in identifying subjects with BRONJ by the presence of stage 0 were calculated based on ROC analysis. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) v.8.0 (SPSS, Chicago, IL). A p-value < 0.05 was considered to represent a statistically significant difference.

Results

Clinical course of BRONJ in patients with breast cancer

The average age of the 247 eligible patients (246 women and one man) was 58.7 years (range = 31–92) and the average BP treatment period was 19.2 months (range = 1–79). Although 166 patients were still alive, 81 cases (32.8%) had already died by June 2010. A total of 44 patients (17.8%) visited the oral surgery department. On the first visit to the oral surgery department, only one (0.4%) patient of the 247 received a diagnosis of BRONJ. On the final evaluation of the same 247 patients, a total of eight (crude incidence rate [CIR] = 3.2%) cases received diagnoses of BRONJ (Figure 2).

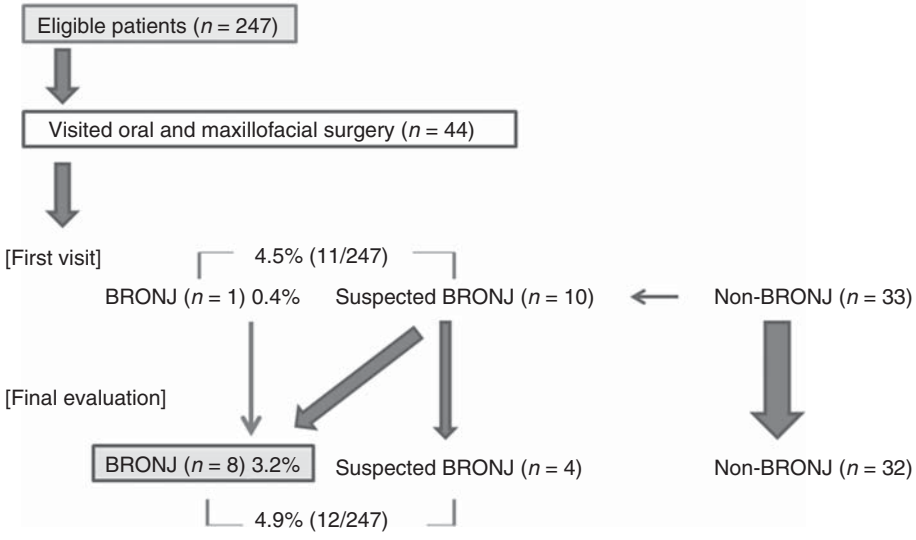

Figure 2. Clinical course of eligible patients. BRONJ occurred in 0.4% ($n = 1$) of subjects at the first visit and in 3.2% ($n = 8$) of subjects during the follow-up period. The majority of BRONJ patients were suspected BRONJ patients at the first evaluation.

Table I. Patient characteristics of BRONJ and non-BRONJ patients.

Variables	Units	BRONJ (n = 8*)		Non-BRONJ (n = 36)		p-value
Age	Years	58.3	(44 < 86)	55.3	(42 < 77)	ns
BP period	Months	30.3	(8 < 66)	26.3	(1 < 66)	ns
BP type	Zoledronate only	4		19		ns
	Zoledronate and others	4		17		
Performance	Stage 0	2		23		ns
	stages 1–4	6		13		
Total protein	g/dl	7	(6.4 < 7.7)	6.9	(5.1 < 7.8)	ns
Remaining teeth	Number	16.5	(1 < 28)	24.1	(0 < 28)	0.006
BP begun, first visit	Month	17.5	(1–29)	13.2	(0–60)	ns
Regular oral monitoring	Yes	0		17		0.013
	No	8		19		
Stage 0	Yes	6		4		0.006
	No	2		32		
Oral hygiene	Fine	1		10		0.070
	Fair	3		23		
	Poor	4		3		

*Patients with suspected BRONJ at the final evaluation are included in the non-BRONJ patient group.
ns, not significant.

Risk factors for BRONJ

There were no significant differences in age, total BPs treatment period, BP treatment period before oral examination, total blood protein level, performance status, BP type or oral hygiene between the BRONJ and non-BRONJ subjects. On the other hand, there were statistically significant differences in the number of remaining teeth, the presence of regular oral monitoring and the presence of stage 0 between the two groups (Table I).

Logistic regression analysis revealed that the OR for identifying patients with BRONJ during follow-up by the presence of stage 0 on the first visit was 24.0 (95% CI = 3.6–161.7). The AUC for identifying subjects with BRONJ by the presence of stage 0 was 0.82 (95% CI = 0.63–1.00) (Figure 3). Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for identifying subjects with BRONJ by the presence of stage 0 was 75.0%, 88.9%, 60.0%, 94.1% and 86.4%, respectively.

Clinical status of patients with BRONJ and suspected BRONJ

Of 12 BRONJ and stage 0 BRONJ patients, the necrotic bone was spontaneously exposed without infection in two, and these were classified as stage 1. In the other 10 patients, BRONJ subsequently developed in six. The average period from first oral examination to bone exposure was 4 months (range = 1–8). When the bone was exposed, the AAOMS stages were either 2 or 3. Subjects with stage

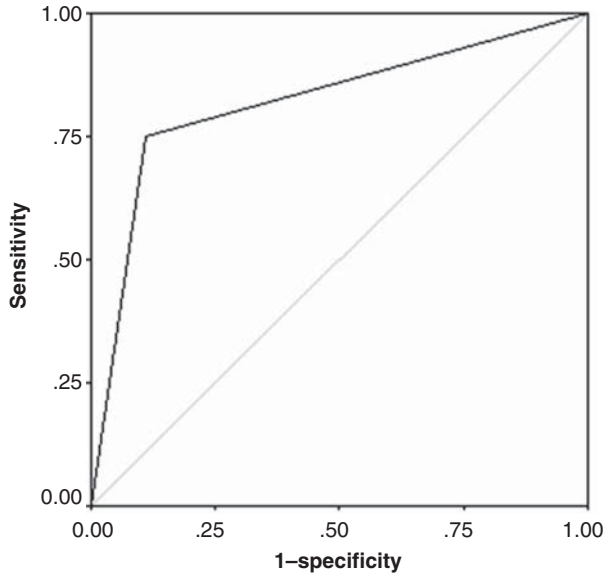

Figure 3. Receiver operating characteristic curve of the suspected BRONJ (stage 0) period. Logistic regression analysis revealed that the odds ratio for identifying patients with BRONJ during follow-up by the presence of stage 0 at the first visit was 24.0 (95% confidence interval [CI] = 3.6–161.7). The area under the curve (AUC) of the receiver operating characteristic (ROC) was 0.82 (95% confidence interval [CI] = 0.63–1.00).

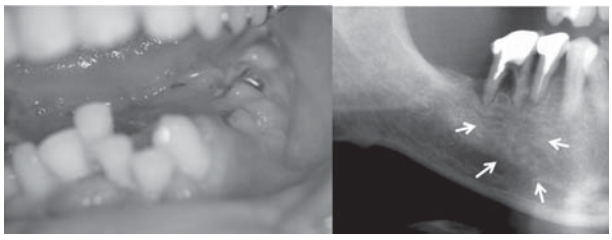

Figure 4. BRONJ symptoms in stage 0 patients. Left photo: Intra-oral view of an acute dental infection case (Case 2). Diffuse swelling and a discharge of pus were observed in the 43–36 area without bone exposure. Right radiograph: Osteosclerotic and lytic findings were observed (arrow) in the 46 and 45 areas (Case 3).

0 BRONJ had persistent acute dental infection, abnormal radiographic findings or both. Sclerotic and osteolytic changes or surface irregularities were observed on radiographs (Figure 4). Half of these 10 cases ($n = 5$) had both dental infection and radiographic abnormalities, but the remaining five did not show any evidence of radiographic abnormalities or clinical signs of infection. All BRONJ and suspected BRONJ patients had not undergone any previous surgical dental procedure at the affected site, except in two cases of tooth defluxion. BRONJ and suspected lesions of the subjects in this study were cured by marginal resection, defluxion and natural healing in only three cases. The average follow-up period of BRONJ after bone exposure was 15.1 months (range = 6–44). A total of 40% of patients had regular oral monitoring ($n = 18/44$). No patients with BRONJ or suspected BRONJ had continued regular oral monitoring (Table II).

Discussion

We set out to clarify the characteristics of the early stages of intravenous BP-related BRONJ, before bone exposure, in patients with breast cancer. Several studies have described the non-exposed variant of BRONJ [9,14–17], but no study has elucidated its frequency or natural history [9]. The AAOMS recently defined the early stages of BRONJ as stage 0, described as cases without clinical evidence of necrotic bone, but presenting with non-specific symptoms or abnormal clinical or radiographic findings. These symptoms include the presence of periapical/periodontal fistula and changes to trabecular patterns [10]. Only one study has reported the status of stage 0 patients [18], but it has not been confirmed whether stage 0 status directly progresses to bone exposure. On the other hand, it has been said that the cumulative incidence of BRONJ increases with time [19]. Several cohort studies have evaluated the cumulative hazard of intravenous BRONJ [19–22], but there are no studies which describe the early stages of BRONJ before bone exposure. In the present cohort, it was possible to ascertain the history and oral status of the patients before bone exposure through our monitoring program. The present results reveal that many local factors could be potential risk factors, and that the stage 0 period is the strongest risk factor for the occurrence of BRONJ on logistic regression and ROC curve analysis. To the best of our knowledge, this study is the first to indicate that stage 0 BRONJ typically progresses to bone exposure.

Tooth extraction has been reported as one of the strongest risk factors for BRONJ [10,19,21,23]. Surgical intervention, including extraction, is not recommended for BP treatment patients in most position papers [3–7]. In many studies, BRONJ occurs after the extraction of teeth due to severe dental disease or around the teeth with active periodontal or periapical disease [10,24,25]. Recently, Aghaloo et al. [26] suggested that periodontal disease and potent BP therapy are sufficient for BRONJ development in rats. However, no clinical study has directly confirmed the relationship between dental infection disease and BRONJ. In addition, the relationship between BRONJ and chronic osteomyelitis is controversial. A previous report recommended that BRONJ should be distinguished from chronic osteomyelitis [4], but other studies [27,28] reported that osteomyelitis was a very strong risk factor for BRONJ. In the present study, the symptoms of stage 0 in cases which progressed to BRONJ were persistent acute dental infection and radiographic abnormalities suspected to be osteomyelitis, but no surgical intervention was performed before the first visit. Dental panoramic radiography is a good screening method for the early detection of BRONJ before bone exposure [29], but it has been found to be of limited use in assessing BRONJ [30]. Computed tomography and magnetic resonance imaging are useful to help to determine the extent of disease [28], but it is difficult to use them regularly for oral monitoring. In the present study, abnormal radiographic findings on dental panoramic radiographs were considered to be sufficient signs of BRONJ, but persistent acute dental infection without radiographic abnormalities alone was also considered to be a sign of BRONJ. We speculated that, although the jaw bones of stage 0 patients already had osteomyelitis, their structure and strength were maintained by BP treatment [31,32]. Therefore, BRONJ may occur directly from dental infection and tooth extraction may only be a trigger of bone exposure. Furthermore, many extraction cases that are a result of uncontrolled severe dental infection may have already progressed to BRONJ, but without showing obvious radiographic changes.

The CIR of intravenous BRONJ in breast cancer patients has been reported to range from 1.2–11.4% [19–22,33–37]. In the present cohort, the frequency of BRONJ on the first visit was 0.4%, but subsequently increased to 3.2% by final evaluation. This result suggests two opposing aspects, namely, that our

Table II. Clinical status of BRONJ and suspected BRONJ patients.

Case	Age (Years)	BPs Period (Months)	BP types*	Stage 0**	X-ray findings	Infection	Site	Bone exposure+	AAOMS stage	Treatment	Follow up period (Months)	Local prognosis†	Systemic prognosis#
1	86	13	Z+O	O	Irregular, osteolytic	-	Lower anterior	O(5)	2	Conservative	8	Non	D
2	44	32	Z+O	O	-	Acute marginal periodontitis	Lower anterior, L premolar	O(5)	3	Extraction	8	Non	D
3	67	33	Z+O	O	Sclerotic, osteolytic	Chronic marginal periodontitis, tooth defluxion	R Upper molar	O(8)	2	Conservative	15	Non	D
4	45	57	Z+O	O	-	Stump tooth, Acute sinusitis	L Upper molar	O(1)	3	Conservative	12	Non	D
5	51	9	z	O	Irregular, osteolytic	Acute marginal periodontitis, tooth defluxion	L Lower premolar	O(1)	2	Conservative	6	Non	A
6	52	41	z	-	-	-	L palate	O(–)	1	Conservative	44	Non	A
7	61	16	z	O	Sclerotic, osteolytic	Periimplantitis	R Lower molar	O(4)	2	Marginal resection	6	Cure	A
8	60	16	z	-	-	-	R Lower molar lingual	O(-)	1	Natural healing	22	Cure	A
9	66	22	z	O	Sclerotic, osteolytic	Acute marginal periodontitis	L Lower premolar			Conservative	6	Non	A
10	59	31	Z+O	O	Sclerotic, osteolytic	Chronic marginal periodontitis	Lower full			Conservative	6	Non	D
11	45	12	z	O	Sclerotic, osteolytic	Acute marginal periodontitis	R Lower molar			Tooth defluxion	12	Cure	A
12	56	25	z	O	-	Exposure of a tooth root	R Lower premolar			Conservative	12	Non	A

*Z, zoledronic acid; Z+O, zoledronic acid and other bisphosphonates (BPs).
**Presence of stage 0 during the follow-up period.
+O, number of months from first appearance of any symptoms of suspected BRONJ after bone exposure.
†Condition of BRONJ; Non, not cured.
#D, Death; A, Arive.

oral monitoring program has contributed to the early recognition of BRONJ, but has not contributed to improvements in treatment outcomes. Several studies indicated that the occurrence of BRONJ decreased after the implementation of dental preventive measures, but did not disappear completely [38,39]. On the other hand, the high success rate of surgical treatments was recently reported [40–43]. If most stage 0 patients progress to BRONJ but BRONJ patients in whom BRONJ was not suspected progressed to BRONJ as in the present study, an early surgical intervention for stage 0 patients could be a reasonable curative option. However, we should note another aspect; namely, that continuing regular oral monitoring in the BP treatment cancer patients was very difficult because of their low level of activities of daily living. The survival time in breast cancer patients after metastasis is relatively long [44]. However, in the present study, 32.8% of subject patients died during the follow-up period and few patients were able to continue regular oral monitoring. Another study of intravenous BP treatment in patients with breast cancer reported a similar survival rate [8]. We should consider the overall conditions in the treatment strategies for BRONJ, especially with regard to surgical procedures.

The present study has several limitations. First, not all patients received an oral examination, which could represent a study bias. We would expect a slightly higher incidence rate in a prospective study design in which every patient has an oral examination, because even asymptomatic BRONJ cases are now frequently recorded [13]. Moreover, breast surgeons followed up the patients and investigated any suspected oral conditions; symptomatic patients must be immediately referred to oral surgeons, as in our monitoring program. The early detection of BRONJ will also save both time and expense. A team approach among physicians and dentists is important for the management of BRONJ [5,6,23]. In our monitoring program, the principal oncologists have a greater role. Furthermore, Hoff et al. [19] reported that the frequency of BRONJ may differ according to geographical region, but almost all of the subject patients of previous studies in breast cancer were Caucasians [19–22,33–37]. Several studies compared the frequency of intravenous BRONJ among different ethnic groups, and it was higher in Caucasians than in African Americans [45,46]. To the best of our knowledge, the present study is the first to show the CIR of intravenous BRONJ incidence in breast cancer patients in a solely Asian population. The results of the present study were consistent with those of other ethnic groups [19–22,33–37].

In conclusion, breast cancer patients given intravenous BP who have signs of stage 0 BRONJ on the first visit may progress to advanced BRONJ during follow-up. Furthermore, our oral monitoring program may contribute to the early detection of BRONJ.

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