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ORIGINAL ARTICLE

Medication-related osteonecrosis of the jaw after tooth extraction in cancer patients: a multicenter retrospective study

T. Hasegawa[1] · S. Hayashida[2] · E. Kondo[3] · Y. Takeda[4] · H. Miyamoto[5] · Y. Kawaoka[6] · N. Ueda[7] · E. Iwata[1,8] · H. Nakahara[9] · M. Kobayashi[10] · S. Soutome[2] · SI. Yamada[3] · I. Tojyo[4] · Y. Kojima[6] · M. Umeda[2] · S. Fujita[4] · H. Kurita[3] · Y. Shibuya[5] · T. Kirita[7] · T. Komori[1] · Japanese Study Group of Co-operative Dentistry with Medicine (JCDM)

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Abstract

Summary Root amputation, immunosuppressive therapy, mandibular tooth extraction, pre-existing inflammation, and longer duration of treatment with bone-modifying agents were significantly associated with an increased risk of medication-related osteonecrosis of the jaw. Hopeless teeth should be extracted without drug holiday before the development of inflammation in cancer patients receiving high-dose bone-modifying agents.

Introduction No studies have comprehensively analyzed the influence of pre-existing inflammation, surgical procedure–related factors such as primary wound closure, demographic factors, and drug holiday on the incidence of medication-related osteonecrosis of the jaw (MRONJ). The purpose of this study was to retrospectively investigate the relationships between these various factors and the development of MRONJ after tooth extraction in cancer patients receiving high-dose bone-modifying agents (BMAs) such as bisphosphonates or denosumab.

Methods Risk factors for MRONJ after tooth extraction were evaluated with univariate and multivariate analyses. The following parameters were investigated in all patients: demographics, type and duration of BMA use, whether BMA use was discontinued before tooth extraction (drug holiday), the duration of such discontinuation, the presence of pre-existing inflammation, and whether additional surgical procedures (e.g., incision, removal of bone edges, root amputation) were performed.

Results We found that root amputation (OR = 22.62), immunosuppressive therapy (OR = 16.61), extraction of mandibular teeth (OR = 12.14), extraction of teeth with pre-existing inflammation, and longer duration (≥ 8 months) of high-dose BMA (OR = 7.85) were all significantly associated with MRONJ.

Conclusions Tooth extraction should not necessarily be postponed in cancer patients receiving high-dose BMA. The effectiveness of a short-term drug holiday was not confirmed, as drug holidays had no significant impact on MRONJ incidence. Tooth extraction may be acceptable during high-dose BMA therapy until 8 months after initiation.

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✉ T. Hasegawa
hasetaku@med.kobe-u.ac.jp

[1] Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

[2] Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

[3] Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, Matsumoto, Japan

[4] Department of Oral and Maxillofacial Surgery, Wakayama Medical University, Wakayama, Japan

[5] Department of Oral Maxillofacial Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

[6] Department of Dentistry and Oral Surgery, Kansai Medical University, Hirakata, Japan

[7] Department of Oral and Maxillofacial Surgery, Nara Medical University, Kashihara, Japan

[8] Department of Oral and Maxillofacial Surgery, Kakogawa Central City Hospital, Kakogawa, Japan

[9] Department of Oral and Maxillofacial Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan

[10] Department of Oral and Maxillofacial Surgery, Shin-Suma General Hospital, Kobe, Japan

Keywords Bisphosphonate · Denosumab · Discontinuation · Drug holiday · MRONJ

Introduction

Bone-modifying agents (BMAs) such as bisphosphonates (BPs) and denosumab (Dmab) inhibit bone resorption and are widely used to treat various bone diseases and bone-associated complications. BMAs have also been used to treat malignancy-induced hypercalcemia and metastatic bone diseases and to reduce skeletal complications [1, 2]. Since Marx [3] first reported BP-related osteonecrosis of the jaw (BRONJ), the condition has been recognized as a complication of invasive procedures performed during BP therapy. Dmab sometimes induces osteonecrosis similar to BRONJ [4]. Therefore, medication-related osteonecrosis of the jaw (MRONJ) is now widely known. The incidence of BRONJ is reported to be higher with the use of intravenous BPs than with oral BPs [5]. Previously, intravenous BPs were only used to treat cancer patients. Recently, osteoporosis has also been managed with intravenous BPs, such as once-yearly infusion of zoledronate [6]. Some studies that have analyzed the risk of BRONJ with intravenous BP therapy have included both cancer patients and osteoporosis patients, although the risk of BRONJ is very different between these patient groups [7, 8].

The incidence of MRONJ after tooth extraction in patients with cancer who are exposed to intravenous BPs ranges from 1.6 to 14.8% [9]. The American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper and a previous Japanese position paper recommend that procedures involving direct osseous injury should be avoided in cancer patients receiving BMA because of the high risk of MRONJ [9, 10]. However, excessive delay in extracting an inflamed tooth increases the risk of MRONJ, so tooth extraction cannot be avoided completely, although tooth extraction itself is the main risk factor for MRONJ [11]. One study proposed that pre-existing inflammation such as periodontal or periapical disease was a risk factor for MRONJ rather than tooth extraction [12]. Some studies have demonstrated a low incidence (0–2.8%) of MRONJ after tooth extraction with new surgical procedures in patients receiving intravenous high-dose BP therapy [13, 14]. Whether unfavorable teeth should be extracted in cancer patients receiving high-dose BMA remains controversial because of these discrepancies in the reported incidence of MRONJ.

In summary, no study has comprehensively analyzed the influence of pre-existing inflammation, surgical procedure–related factors such as primary wound closure, demographic factors, and drug holiday on MRONJ incidence. We hypothesized that pre-existing inflammation and surgical procedure–related factors, such as primary wound closure, influence the occurrence of MRONJ. In this study, we investigated the multivariate relationships among these various MRONJ risk factors.

Methods

This was a nonrandomized, multicenter retrospective cohort study. This multicenter validation study included pooled individual patient data from ten institutions belonging to the Japanese Study Group of Co-operative Dentistry with Medicine (JCDM). Between January 2008 and December 2016, tooth extractions were performed at our institutions in 174 patients receiving intravenous BP or Dmab therapy. A total of 151 dental extractions were performed in 89 patients receiving intravenous BP or Dmab therapy for osteoporosis. Post-extraction MRONJ was diagnosed in one tooth (0.7%) in one of these patients. Patients with osteoporosis were excluded from this study. A total of 163 dental extractions performed in 85 cancer patients (34 men and 51 women) receiving high-dose BMA were included in this study. The mean age of the patients was 64.5 ± 11.5 years (range 39–90 years).

This study was approved by the institutional review board of Kobe University Graduate School of Medicine and by the institutional review boards of the respective hospitals. Before surgery, each patient was informed about MRONJ and other extraction-associated risks and gave consent for treatment. The definition of MRONJ was taken from the AAOMS position paper [9]. MRONJ can be diagnosed by the following three characteristics: (1) current or previous treatment with antiresorptive or antiangiogenic agents, (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks, and (3) no history of radiation therapy to the jaws or obvious metastatic disease of the jaw. Demographics of all patients were investigated, including type and duration of high-dose BMA treatment; whether or not high-dose BMA was discontinued before tooth extraction (drug holiday); the use of any additional surgical procedures such as incision, bone removal, tension-relieving incision, root amputation, and suturing; whether antibiotics were administered before extraction; the presence of pre-existing inflammation; bone loss around the tooth; the duration of follow-up; and the time to primary wound healing without evidence of infection. The definition of discontinuation was a drug holiday of more than 2 months before extraction. The definition of pre-existing inflammation was clinical symptoms (pain, swelling, redness, or purulent discharge) requiring administration of antibiotics within 2 weeks before tooth extraction. The reason for tooth extraction, the number of extracted teeth, and the site of tooth extraction were also investigated. Alveolar bone loss was measured at the mesial and distal surfaces of the tooth between the apex of the root and the cervical margin using orthopantomography. Bone loss around a tooth was defined as follows: (average length) / (distance between root apex and

cervical margin) × 100 ≥ 50%. Details of these characteristics and patient demographics are listed in Table 1. The data were introduced into a multiple logistic regression model, in which patients were divided according to the number of teeth extracted (single vs. multiple), the grade of tooth mobility (0 vs. 1, 2, or 3), the state of the wound (open vs. closed), the duration of administration of high-dose BMA (≥ 8 months vs. < 8 months), and the Eastern Cooperative Oncology Group performance status (0 or 1 vs. 2 or 3) [15]. This study investigated the incidence of MRONJ as the primary outcome. Possible development of MRONJ was noted and (if present) classified into different stages (0–3) according to the criteria defined in the AAOMS position paper [9]. Stage 0 is characterized by no clinical evidence of necrotic bone, with nonspecific clinical findings, radiographic changes, and symptoms. Stage 1 features exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection. Stage 2 features exposed and necrotic bone or fistulas that probe to bone associated with infection as evidenced by pain and erythema in the region of exposed bone, with or without purulent drainage. Stage 3 is characterized by exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and more than one of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus of the mandible, maxillary sinus, and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor [9].

Statistical analysis

SPSS 22.0 (SPSS Inc., Chicago, IL) and Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan) were used for statistical analyses. The association of each variable with MRONJ was analyzed with the Mann–Whitney *U* nonparametric test for ordinal variables and with Fisher's exact test or the chi-square test for categorical variables. Probabilities of less than 0.05 were accepted as significant. All variables associated with MRONJ were introduced into a multiple logistic regression model. Forward stepwise algorithms were used, with the rejection of those variables that did not fit the model significantly. Odds ratios (OR) and 95% confidence intervals (CIs) were also calculated.

The discriminatory ability of the duration of administration of high-dose BMA as an indicator of possible MRONJ events was evaluated with a receiver operating characteristic (ROC) curve. This ROC curve was used to determine the cutoff values for clinical tests. The area under the resulting curve (AUC) measures the accuracy of this discrimination, ranging from 0.5 to 1. The cutoff value was chosen to minimize the number of false-positive and false-negative results.

Table 1 Characteristics and demographics of patients receiving high-dose bone-modifying agents (BMAs)

Variables (overlapping distribution)	Number (%)
Number of patients	85 (100.0)
Sex	
Male	34 (40)
Female	51 (60)
Age (years)	
Range (years)	39–90
Mean ± SD	64.5 ± 11.5
Performance status	
0	46 (54.1)
1	36 (30.6)
2	12 (10.6)
3	4 (3.5)
Unknown	4 (1.2)
Smoking history	
Smoker	16 (31.3)
Nonsmoker	55 (64.7)
Unknown	14 (16.5)
Type of BMA	
Zoledronate	46 (54.1)
Denosumab	31 (36.5)
Zoledronate/denosumab	6 (7.1)
Alendronate/denosumab	1 (1.2)
Risedronate/denosumab	1 (1.2)
Duration of high-dose BMA administration (months)	
Range	1–60
Mean ± SD	14.7 ± 13.8
Patients with MRONJ	
Total	25 (29.4)
Stage 0	1 (4.0)
Stage 1	11 (44.0)
Stage 2	9 (36.0)
Stage 3	4 (16.0)

Results

Post-extraction MRONJ was diagnosed in 41 teeth (25.2%) in 25 patients. Of these, one patient (4.0%) was at stage 0, 11 (44.0%) were at stage 1, nine (36.0%) were at stage 2, and four (16.0%) were at stage 3. No significant differences in MRONJ incidence were observed according to demographic factors such as age, sex, smoking history, or performance status (Table 2). The duration of high-dose BMA administration among patients with MRONJ was significantly longer than that among patients without MRONJ ($p < 0.001$) (Table 2). There was a significant difference in MRONJ incidence between patients treated for ≥ 8 months versus those treated for < 8 months with high-dose BMA.

Table 2 Characteristics of teeth according to the presence of MRONJ

Variables	MRONJ		*p* value
	Present, *n* (%)	Absent, *n* (%)	
Number of teeth	41 (25.2)	122 (74.8)	
Sex			
Male	17 (41.5)	48 (39.3)	0.855*
Female	24 (58.5)	74 (60.7)	
Age			
Range (years)	42–90	39–85	
Mean ± SD	66.1 ± 13.1	65.0 ± 10.9	0.899**
Smoking history			
Yes	12 (29.3)	23 (18.9)	0.177*
No	23 (56.1)	82 (67.2)	
Unknown	6 (14.6)	17 (13.9)	
Performance status			
0 or 1	32 (78.1)	105 (86.1)	0.355*
2 or 3	8 (19.5)	17 (13.9)	
Unknown	1 (2.4)	0 (0)	
Duration of high-dose BMA administration			
Range (months)	1–60	1–42	
Mean ± SD	20.9 ± 13.2	12.9 ± 12.0	< 0.001**
≥ 8 months	37 (90.2)	58 (58.3)	< 0.001*
< 8 months	4 (9.8)	55 (36.2)	
Unknown	0 (0)	9 (5.5)	
≥ 1 year	34 (82.9)	55 (45.6)	< 0.001*
< 1 year	7 (17.1)	58 (47.5)	
Unknown	0 (0)	9 (5.5)	
Comorbidity or drug-induced risk factor			
Diabetes mellitus			
Yes	4 (9.8)	14 (11.5)	0.206*
No	37 (90.2)	108 (88.5)	
Use of Dmab			
Yes	20 (48.8)	53 (43.4)	0.844*
No	21 (51.2)	69 (56.6)	
Steroid therapy			
Yes	3 (7.3)	9 (7.4)	1.000*
No	38 (92.7)	113 (92.6)	
Immunosuppressive therapy			
Yes	3 (7.3)	1 (0.8)	0.049*
No	38 (92.7)	121 (99.2)	
Additional chemotherapy			
Yes	23 (56.1)	76 (62.3)	0.843*
No	12 (29.3)	46 (37.7)	
Unknown	6 (14.6)	0 (0)	
Drug holiday before tooth extraction			
Yes	17 (41.5)	41 (33.6)	0.451*
No	24 (58.5)	81 (66.4)	
Reason of tooth extraction			
Periapical periodontitis (per)	24 (58.5)	42 (34.4)	
Per + radicular cyst	1 (2.4)	1 (0.8)	
P4 periodontitis	8 (19.5)	42 (34.4)	
C4 caries	1 (2.4)	32 (26.2)	
Pericoronitis	6 (14.6)	1 (0.8)	
Root fracture	1 (2.4)	4 (3.3)	
Periapical periodontitis			
Yes	25 (61.0)	43 (35.2)	0.006*
No	16 (39.0)	79 (64.8)	
P4 periodontitis			
Yes	8 (19.5)	42 (34.4)	0.081*
No	33 (80.5)	80 (65.6)	
Jawbone			
Maxillary	10 (24.4)	77 (63.1)	< 0.001*
Mandibular	31 (75.6)	45 (36.9)	
Site of tooth extraction			
Anterior region	11 (26.8)	38 (31.1)	0.696*
Molar region	30 (73.2)	84 (68.9)	

Table 2 (continued)

Variables	MRONJ		*p* value
	Present, *n* (%)	Absent, *n* (%)	
Bone volume around tooth			
Adequate alveolar bone volume	19 (46.3)	64 (52.5)	1.000*
Bone loss	18 (43.9)	58 (47.5)	
Unknown	4 (9.8)	0 (0)	
Grade of tooth mobility			
0	20 (48.8)	39 (32.0)	0.039***
1	3 (7.3)	21 (17.2)	
2	5 (12.2)	13 (10.7)	
3	8 (19.5)	49 (40.2)	
Unknown	5 (12.2)	0 (0)	
Pre-existing inflammation			
Yes	37 (90.2)	72 (59.0)	0.001*
No	4 (9.8)	50 (41.0)	
Preoperative antibiotics administration			
Yes	15 (36.6)	36 (29.5)	0.438*
No	26 (63.4)	86 (70.5)	
Number of teeth extracted			
Single	14 (34.2)	33 (27.0)	0.428*
Multiple	27 (65.8)	89 (73.0)	
Additional surgical procedure			
Incision			
Yes	18 (43.9)	43 (35.2)	0.354*
No	23 (56.1)	79 (64.8)	
Bone removal			
Yes	12 (29.3)	28 (23.0)	0.410*
No	29 (70.7)	94 (77.0)	
Root amputation			
Yes	9 (22.0)	4 (3.3)	< 0.001*
No	32 (78.0)	118 (96.7)	
Wound state after extraction			
Open	17 (41.5)	42 (34.4)	0.361***
Closed with suture	22 (53.7)	63 (51.6)	
Completely closed with relaxation incision or removal of bone edge	2 (4.8)	15 (12.3)	
Unknown	0 (0)	2 (1.6)	

*: Fisher's exact test. **: Mann–Whitney U test. ***: Chi-squared test

Immunosuppressive therapy was significantly associated with the development of MRONJ ($p = 0.049$) (Table 2). However, there were no significant differences in the development of MRONJ between BP (21 of 90 teeth; 23.3%) and Dmab (20 of 73 teeth; 27.4%). Similarly, patients with diabetes mellitus or other drug-induced risk factors and those who had a drug holiday before tooth extraction did not have significantly different rates of MRONJ than patients without these factors (Table 2). Extraction of mandibular teeth was a significant predictor of MRONJ ($p < 0.001$), as was extraction of teeth with periapical periodontitis ($p = 0.006$) (Table 2). However, there were no significant differences in the development of MRONJ according to the site of extraction (anterior vs. posterior region) or the number of teeth extracted. A significantly higher proportion of the teeth extracted in MRONJ cases did not have mobility, compared with the proportion among extractions that did not result in MRONJ ($p = 0.039$) (Table 2). Extraction of a tooth with pre-existing inflammation was a significant predictor of MRONJ ($p < 0.001$) (Table 2). Procedure-related factors such as incision, bone removal, and wound status were not significant risk factors for MRONJ (Table 2). However, root amputation was significantly associated with MRONJ development (Table 2). MRONJ was less prone to develop in patients who had complete wound closure with tension-relieving incisions and/or removal of bone edges, although the differences were not significant.

Applying a logistic regression model and forward stepwise algorithms, we found that root amputation (OR = 22.62), immunosuppressive therapy (OR = 16.61), extraction of mandibular teeth (OR = 12.14), extraction of teeth with pre-existing inflammation, and longer duration (≥ 8 months) of high-dose BMA (OR = 7.85) were all significantly associated with MRONJ (Table 3).

The AUC of the ROC curve was 0.68, a value generally considered to be inaccurate. Maximization of the harmonic mean of the specificity and sensitivity put the duration of high-dose BMA cutoff for predicting post-extraction MRONJ at 8 months (Fig. 1). The resulting sensitivity was 0.90, and the specificity was 0.49.

Table 3 Results of multivariate logistic regression analysis of the risk factors for MRONJ

Variable	*p* value	Odds ratio	95% CI	
			Lower	Upper
Root amputation	0.019	22.622	1.654	309.483
Immunosuppressive therapy	0.033	16.614	1.256	219.834
Mandibular location	< 0.001	12.141	3.085	47.783
Pre-existing inflammation	0.029	11.363	1.291	100.02
Longer duration of high-dose BMA (≥ 8 months)	0.007	7.853	1.765	34.942

CI confidence interval

Discussion

Generally, MRONJ is associated with BMA in cancer patients and not with oral administration in osteoporosis patients [9]. The incidence of MRONJ after tooth extraction in patients with cancer who receive intravenous BPs ranges from 1.6 to 40.0% [9, 11, 16, 17]. Gaudin et al. [18] reported that the incidence of MRONJ was 0% to 51.9% among patients receiving intravenous BPs. In contrast, some studies have reported low MRONJ incidence rates (0–2.8%) after tooth extraction with new surgical procedures in patients receiving intravenous BP therapy [7, 8, 13, 14]. However, some studies investigating the risk of BRONJ with intravenous BP therapy have evaluated populations that included both cancer patients and osteoporosis patients [7, 8]. Also, several publications have reported a small number of cases of intravenous BP use [15, 19, 20]. These variations in study design explain the great discrepancies in the reported incidence rates. Because of these discrepancies, it remains controversial whether unfavorable teeth should be extracted in cancer patients receiving high-dose BMA.

A large review by Filleul et al. [21] concluded that tooth extraction was the main triggering factor in 67% of BRONJ cases. Tooth extraction is believed to be a major risk factor for the development of MRONJ [9, 16]. Therefore, a previous BRONJ position paper from the Allied Task Force Committee of the Japanese Society for Bone and Mineral Research suggested that nonsurgical treatments should be performed rather than surgical treatments such as tooth extraction if dental treatments are desperately required [10]. The AAOMS position paper also recommended that procedures that involve direct osseous injury should be avoided in cancer patients receiving BMA because of the high risk of MRONJ [9]. According to these guidelines, surgeons might treat even severely infected teeth using a nonsurgical approach whenever possible. In this study, the incidence of MRONJ after tooth extraction was 25.2%, which is higher than rates in previous studies. Our MRONJ cases might have included patients who had already developed MRONJ before tooth extraction, because it is difficult to distinguish early, stage 0 MRONJ from tooth infection. In previous studies with low incidence rates of MRONJ after tooth extraction, patients with clinical symptoms might have been excluded as stage 0 MRONJ according to exclusion criteria [7, 8, 13, 14].

Pre-existing inflammation is a risk factor for MRONJ [12, 22–24]. Katsarelis et al. [25] proposed that infection could be the factor initiating the development of MRONJ, rather than low bone turnover. Macrophages are crucial in the prevention of local infection; macrophages exposed to BPs lose their ability to activate and respond to infection [25, 26]. Soutome et al. [27] reported that the presence of symptoms of clinical infection was a risk factor for MRONJ rather than tooth extraction itself. In this study, 90.2% of all MRONJ cases had pre-existing inflammation. In multivariate analysis, pre-existing inflammation (OR = 11.36) and immunosuppressive therapy (OR = 16.61) were found to be significant risk factors for MRONJ. However, the role of immunosuppressive therapy should be carefully considered because of the small population size ($n = 4$). The results of this study suggest that tooth extraction should not necessarily be postponed in cancer patients receiving high-dose BMA. Nonrestorable teeth and those with a poor prognosis should be extracted before the development of inflammation, especially in the case of cancer with an expected longer prognosis.

Theoretically, long-term duration of BMA carries a high risk of MRONJ [9, 12, 24]. Saad et al. [22] reported that the incidence of MRONJ was 0.5% to 0.8% at 1 year and 1.0% to 1.8% at 2 years to 3 years among cancer patients receiving zoledronate or Dmab therapy; the median duration of drug exposure before MRONJ development was 14 months for both treatment groups. One report demonstrated that high-dose BMA had been administered for more than 13 months in 12 (92.3%) of 13 MRONJ patients [24]. Bodem et al. [28] reported that the duration of intravenous BP therapy in all BRONJ cases after tooth extraction was more than 11 months. In this study, longer duration of high-dose BMA was found to be a significant risk factor for MRONJ in multivariate analysis (OR = 7.85). The cutoff value for the duration of high-dose BMA that increased the risk of MRONJ was 8 months, based on the results of the ROC curve. Therefore, tooth extraction

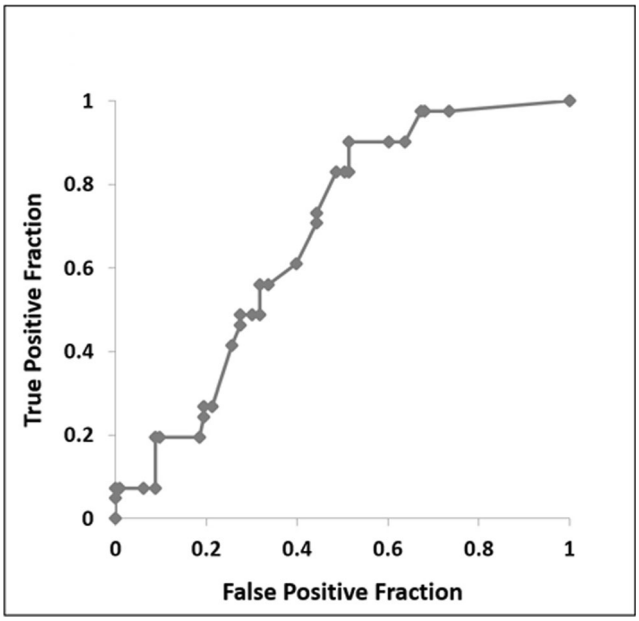

Fig. 1 ROC curve of the duration of administration of BMA as an indicator of possible MRONJ events

may be acceptable during high-dose BMA administration until 8 months after initiation. However, patients should be instructed by physicians to undergo oral examination by dentists.

The discontinuation of oral BPs in osteoporotic patients has been controversial. Recently, we demonstrated multivariate relationships among the various risk factors for MRONJ after tooth extraction in patients receiving oral BPs [29]. The rate of post-extraction MRONJ was 1.7% among 2458 dental extractions. In that study, the effectiveness of a short-term drug holiday (2 months) was not confirmed because drug holidays had no significant impact on MRONJ incidence [29]. However, data are inadequate regarding the effect of discontinuing high-dose BMA before necessary invasive dental treatments [9]. In principle, tooth extraction should be performed without discontinuation of treatment in cancer patients, because high-dose BMA administration often cannot be discontinued for the management of skeletal-related events. Surprisingly, high-dose BMA was discontinued in 58 teeth (35.6%) of 41 patients in this study. The reason for this finding might be the recommendation of a previous position paper that, "if possible, it would be desirable that BP be discontinued for 2–3 months before dental treatment under these circumstances" [10]. In this study, the effectiveness of a short-term drug holiday was not confirmed, as drug holidays had no significant impact on MRONJ incidence. BPs retained in the bone have a terminal half-life of many years [30], so discontinuation of BP therapy for a few months (a drug holiday) will have little effect on the BP already incorporated into the bone [31]. Therefore, other factors such as pre-existing inflammation may be risk factors for MRONJ, rather than the continuation of high-dose BMA before or after tooth extraction. Similarly, the effectiveness of discontinuation was not confirmed in subanalysis of Dmab cases alone (data not shown), although Dmab has a shorter half-life than BPs. However, this result should be carefully considered because of the small population size. We will investigate Dmab as sole therapy in more cases in a future study.

Several studies have reported that mandibular location is an anatomic risk factor for MRONJ [9, 22, 28]. However, other studies failed to confirm this finding [12, 18]. Among patients receiving oral BPs in our previous study, the mandible did not have a higher risk of MRONJ after tooth extraction than the maxilla [29]. However, among cancer patients receiving high-dose BMA in the present study, we found that the mandible had a significantly higher risk of developing MRONJ than the maxilla (OR = 12.14). The higher incidence of MRONJ in the mandible may be explained by the higher rate of remodeling in the mandible, which is twice that in the maxilla and approximately six times that in the femur [32]. Therefore, the reason for the higher incidence of MRONJ in the mandible may be that the higher remodeling in the mandible is strongly suppressed by high-dose BMA.

Several investigators have reported high success rates in tooth extractions performed with post-operative smoothing of sharp bony edges and thorough mucosal wound closure [13, 18, 33, 34]. In multivariate analysis, we found that root amputation was a significant risk factor for the development of MRONJ (OR = 22.62). However, this result was affected by the extraction of wisdom teeth and the persistence of a bony edge, where root amputation was more common. Our previous study in MRONJ patients demonstrated that the most effective treatment for MRONJ was extensive surgery with removal of the necrotic and surrounding bone and primary wound closure [35]. In this study, the incidence of MRONJ was lowest when the wound was completely closed with a tension-relieving incision and/or removal of sharp bone edges, although the differences were not significant. Therefore, we recommend post-extraction removal of bone edges and mucosal wound closure. However, this study had some confounding factors because of its retrospective nature. Further prospective studies are necessary to provide definitive scientific evidence for these recommendations.

In conclusion, we successfully demonstrated the multivariate relationships among the various risk factors for MRONJ after tooth extraction in cancer patients receiving high-dose BMA. Root amputation, immunosuppressive therapy, extraction of mandibular teeth, extraction of teeth with pre-existing inflammation, and longer duration of high-dose BMA (≥ 8 months) were all significantly associated with the development of MRONJ. The results of this study suggest that tooth extraction should not necessarily be postponed in cancer patients receiving high-dose BMA. The effectiveness of a short-term drug holiday was not confirmed, as drug holidays had no

significant impact on MRONJ incidence. Tooth extraction may be acceptable during high-dose BMA therapy until 8 months after initiation.

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Compliance with ethical standards

Conflicts of interest None.

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