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PERSPECTIVE

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

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Abstract Bisphosphonates (BPs) have been widely, efficiently, and safely used for the treatment of osteoporosis, malignant hypercalcemia, bone metastasis of solid cancers, and multiple myeloma bone diseases. Accumulating recent reports describe that surgical dental treatments in patients with cancer or osteoporosis who have been receiving intravenous or oral BPs are associated with osteonecrosis of the jaw (bisphosphonate-related osteonecrosis of the jaw, BRONJ). The accurate incidence, clinical backgrounds, and pathogenesis of BRONJ have been unclear and appropriate approaches for prevention and treatment have not been established to date. To address the current situation of BRONJ in Japan, the "Allied Task Force Committee of Bisphosphonate-Related Osteonecrosis of the Jaw," consisting of physicians specializing in bone biology, orthopedic surgery, rheumatology, obstetrics/gynecology, and medical oncology and dentists specializing in oral surgery, periodontology, dental radiology, and oral pathology, was organized. The committee attempted to propose a standard position paper for the treatment of BRONJ. The committee expects that this proposal will provide objective and correct scientific information on BRONJ and will serve as a reference for conducting dental procedures for patients receiving BPs

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and in designing prevention and treatment of BRONJ. However, because this position paper is not based on direct clinical evidence, it should be used as a reference, and a decision on treatment in each case should be made after an extensive discussion among physicians, dentists/oral surgeons, and the patients.

Keywords Bone resorption · Osteoclasts · Oral bacteria · Osteomyelitis · Team care system

Objectives of the position paper

Bisphosphonates (BPs) are first-line drugs for treatment of osteoporosis worldwide [1]. BPs have been also effectively used for the treatment of hypercalcemia associated with malignant tumors, bone metastasis of solid cancer, and multiple myeloma bone diseases. Furthermore, the usefulness of BPs for metabolic diseases in which bone mass is reduced has been shown. Recently, reports are accumulating that osteonecrosis of the jaw has been infrequently observed following surgical dental treatments such as tooth extraction in patients with cancer or osteoporosis who have been treated with a BP (bisphosphonate-related osteonecrosis of the jaw, BRONJ), although the precise role of BP in BRONJ is unknown. Because many BRONJ cases have been reported in Japan as well, development of appropriate management regimens for this pathological condition is a matter of urgency. However, the accurate incidence, clinical background, and pathogenesis of BRONJ have been unclear, and appropriate approaches for prevention and treatment have not been established, causing confusion among physicians, dentists, pharmacists, and patients.

To address the current situation of BRONJ in Japan, the "Allied Task Force Committee of Bisphosphonate-Related Osteonecrosis of the Jaw" was organized by physicians specializing in bone biology, orthopedic surgery, rheumatology, obstetrics/gynecology, and medical oncology and dentists specializing in oral surgery, periodontology, dental radiology, and oral pathology through collaboration of the Osteoporosis Society Japan, the Japanese Society for Bone and Mineral Research, the Japanese Society of Periodontology, the Japanese Society for Oral and Maxillofacial Radiology, and the Japanese Society of Oral and Maxillofacial Surgeons. The objective of this committee is to propose a standard position paper for the treatment of BRONJ through insightful discussion of BRONJ from various perspectives based on the currently available domestic and overseas literature. The committee expects that this proposal will provide objective and correct scientific information on BRONJ and will serve as a reference for conducting dental procedures for patients receiving BPs and in designing prevention and treatment of BRONJ. However, since because very few prospective randomized clinical studies on BRONJ have been conducted domestically or internationally to date, the committee would like to note that this position paper is not based on direct clinical evidence. Accordingly, the proposed position paper should be used as a reference, and a decision on treatment in each case should be made after an extensive discussion and review of the case among physicians, dentists/oral surgeons, and the patient.

Bisphosphonate-related osteonecrosis of the jaw

The reason that BRONJ develops only in jawbones could be the unique anatomical characteristics of the jawbone compared to other bones.

Anatomical and clinical characteristics of the jawbones

1. Because jawbones hold teeth that break through the epithelium, infectious sources in the oral cavity may directly affect the jawbones (Fig. 1).
2. Because the jawbones are covered with only thin mucosal and periosteal membranes, damage of these oral membranes by physiological actions such as mastication readily causes infection in the underlying jawbones [2].
3. There are 10^{11}–10^{12} resident bacteria of more than 800 types in the oral cavity as a source of infection. The oral cavity provides an ideal environment for the proliferation of these bacteria [2].
4. The jawbones may have an increased blood supply and a high bone turnover compared to other long bones. Turnover of the mandibular alveolar bone is thought to be ten times higher than that of long bones such as the fibula [3]. It should be noted that this idea is controversial. Other studies report that bone turnover is highest in the femur, followed by the mandibular bone and then the maxillary bone [4].
5. Because mandibular bone has thicker and dense cortical bone and richer bone marrow than maxillary bone, the bone remodeling rate may be higher [4]. Therefore, BRONJ is more likely to develop in the mandibular bone than in the maxillary bone.
6. Inflammation can readily spread into the jawbones via infectious dental diseases (caries, dental pulpitis, periapical lesions, and periodontal diseases) (see Fig. 1).
7. The surface of the jawbones is directly exposed to the oral cavity and is readily infected following surgical dental treatment such as tooth extraction [2].

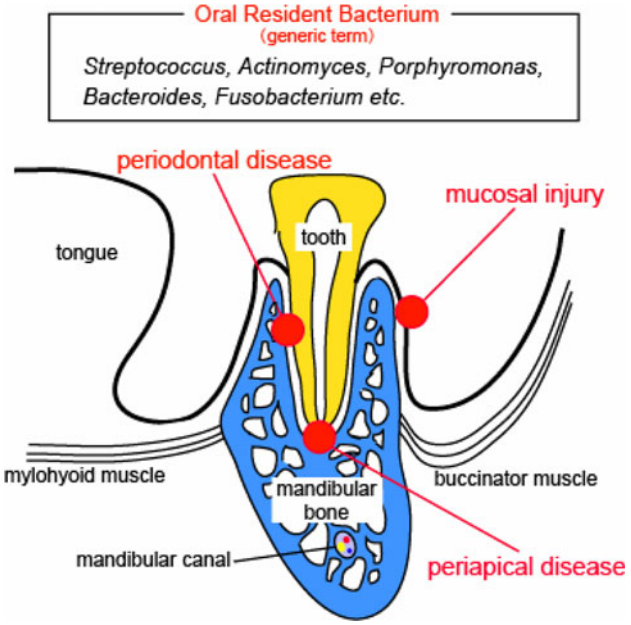

Fig. 1 Anatomical and clinical characteristics of the jawbones. There are 10^{11}–10^{12} resident bacteria of more than 800 types in the oral cavity. Jawbones hold teeth that break through the epithelium, leaving the surface of the jawbones directly exposed to the oral cavity. Moreover, infectious sources in oral cavity may directly affect the jawbones following surgical dental treatments such as tooth extraction. As the jawbones are covered only with thin mucosal and periosteal membranes, injuries of these oral membranes by physiological actions such as mastication readily cause infection in the underlying jawbones. Inflammation can readily spread into the jawbones via dental infectious diseases including periapical lesions and periodontal disease

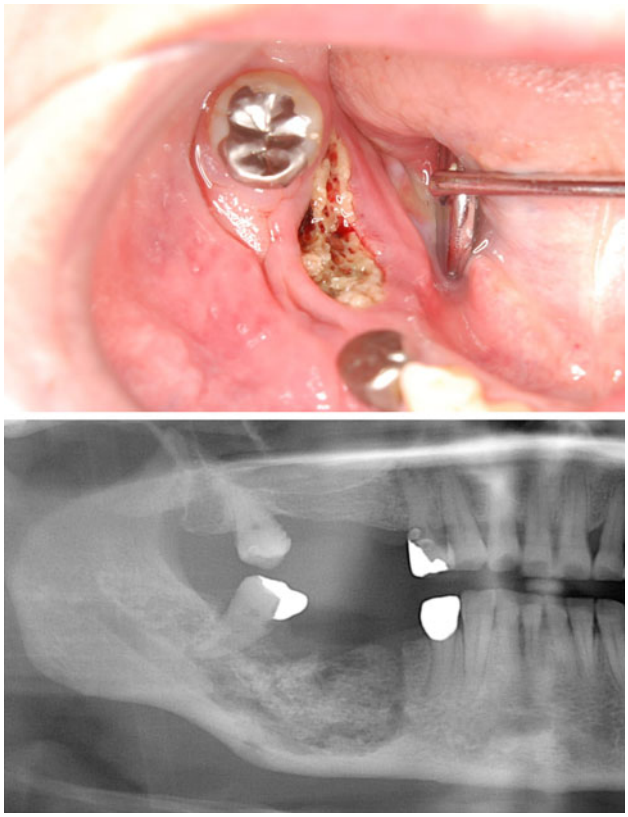

Fig. 2 Macroscopic (*upper panel*) and radiographic (*lower panel*) views of representative bisphosphonate-related osteonecrosis of the jaws (BRONJ). Exposed necrotic bone is seen at the lingual side of the mandibular right second molar. A lesion with osteolysis and osteosclerosis extends from second molar to first premolar region on the panoramic radiograph

Definition, diagnosis, symptoms, and differential diagnosis of BRONJ

Definition and diagnosis

In 2007, the American Association of Oral and Maxillofacial Surgeons (AAOMS) [5] proposed that BRONJ can be diagnosed when a case meets the following three conditions:

1. The patient is currently receiving or has previously been treated with BP.
2. The patient has had exposed necrotic bone in the maxillofacial area for longer than 8 consecutive weeks.
3. The patient has no medical history of radiation therapy for the jawbones.
4. This definition is unchanged in the revised AAOMS position paper published in 2009 [6]. This committee adopts the definition and diagnostic criteria for BRONJ as stated by the AAOMS.

Symptoms

The clinically prominent findings for diagnosis of BRONJ are the presence of exposed alveolar bone in the maxilla and/or mandible (Fig. 2). Other clinical symptoms often seen in BRONJ are shown in Table 1. Among these symptoms, the abnormal sensation in the lower lip (Vincent's symptom) is derived from dysfunction of the inferior alveolar nerve. Otto et al. [7] reported that Vincent's symptom was an early symptom of BRONJ that occurs before exposure of the bone. The AAOMS classified BRONJ cases into four groups according to severity in their revised position paper. Similarly, this committee proposes a four-stage classification based on the current situation in Japan (Table 2). Stage 3 BRONJ is often observed in patients under intravenous BP therapy. BRONJ that is more severe than stage 2 is rarely found in patients receiving oral BPs [8].

Differential diagnosis

The diseases that require differential diagnosis from BRONJ are dry socket (alveolar osteitis), sinusitis,

Table 1 Additional signs and symptoms associated with bisphosphonate-related osteonecrosis of the jaw (BRONJ)

Pain
Swelling
Paresthesia
Suppuration
Soft tissue ulceration
Intraoral fistula
Extraoral fistula
Loosening of teeth
Radiographic lesions: radiolucent, radiopaque, or mixed

Modified from Khosla et al. [32]

Table 2 Staging of BRONJ

Stage of alarm	
Stage 0	No apparent necrotic/exposed bone
	Hypesthesia or anesthesia of lower lip (Vincent's symptom)
	Intraoral fistula
	Deep periodontal pocket
	Small osteolytic lesions on radiograph
Stage 1	Necrotic/exposed bone
	Asymptomatic
	No infection
Stage 2	Necrotic/exposed bone
	Infection (pain, erythema)
	With or without purulent discharge
Stage 3	Stage 2 plus
	Extending necrotic/exposed bone
	Pathologic fractures
	Extraoral fistula
	Oral antral/oral nasal communication
	Extending osteolysis

Modified from Ruggiero et al. [6]

gingivitis, periodontitis, caries, periapical lesions, temporomandibular joint disorder, and tumor of the jaw. Possible metastasis of a primary tumor to the jawbones is always kept in mind, particularly in cancer patients. In addition, diseases associated with exposed bone should be also considered if there is no history of BP treatment (Table 3). Differentiation of BRONJ from chronic osteomyelitis of the jaw is extremely difficult.

Dry socket If a blood clot is not formed in the tooth extraction wound and the bone surface continues to be exposed with sharp pain, the disease is referred to as dry socket (alveolar osteitis) [9]. Because dry socket after tooth extraction in BP-treated patients may progress into BRONJ, immediate treatment is required in such cases.

Table 3 Conditions associated with exposed bone but unrelated to bisphosphonate (BP) use

Trauma
Odontogenic osteomyelitis
Herpes zoster infection associated with osteonecrosis
Benign sequesteration of the lingual plate
Human immunodeficiency virus (HIV)-associated necrotizing ulcerative periodontitis
Primary jawbone tumors
Cancer metastasis to jawbone

Modified from Khosla et al. [32]

Reported incidence of BRONJ

The exact incidence of BRONJ is unknown and has not been investigated in Japan at the moment. However, it is evident that the incidence of osteonecrosis of the jaw (ONJ) associated with parenteral BPs is higher than that with oral BPs.

Incidence of BRONJ associated with administration of intravenous BPs for treatment of malignant tumors

Intravenous BPs are widely used for multiple myeloma bone diseases and bone metastases. Woo et al. [10] reported that 46.5% of 368 BRONJ cases are patients with multiple myeloma and 38.8% are patients with metastatic breast cancer. The incidence of parenteral BP-related BRONJ is 0.8–1.2% on average [11], but the incidence increases up to 21% after BP administration for 3 years or more [10]. According to the Surveillance, Epidemiology, and Ends Results (SEER) Program case-control study (14,349 patients treated with an intravenous BP and 28,698 not treated with BP), the risk of jawbone and facial bone surgery was 3.15 times higher and that of inflammation in the jawbone and osteomyelitis was 11.48 times higher in patients treated with BP. These data gave a cumulative risk of 5.48% at 6 years in BP-treated patients compared to 0.3% in patients not treated with a BP [12]. A recent prospective follow-up study including a relatively small number of subjects showed that BRONJ developed in 22 of 80 patients (28%) after a median dosing period of 32 months [13]. Another study reported that 17 of 252 patients (6.7%) developed BRONJ and that the cumulative incidences after 2 and 4 years were 3% and 11% in all patients and 7% and 21% in zoledronic acid-treated patients [14], respectively.

Because zoledronic acid shows the highest incidence of BRONJ [15] and the shortest administration period before development of BRONJ among BPs (12–18 months for zoledronic acid and 24 months for pamidronate) [16–18], patients treated with zoledronic acid who undergo surgical

dental procedures should be cautiously managed and followed up. The incidence of BRONJ is significantly lower when zoledronic acid is administered once every 6 months (4 mg intravenously) for prevention of postoperative relapse or bone mass reduction (0 case in 899 patients after 48 months and 1 suspected case in 300 patients after 36 months [19, 20].

Incidence of BRONJ associated with BP administration for treatment of osteoporosis

As the accurate number of patients treated with an oral BP is unknown, determination of the precise incidence of BRONJ is extremely difficult. However, an incidence was calculated based on the results of a prospective randomized controlled study in which 7,714 cases were investigated to evaluate the effects of zoledronic acid (intravenous administration of 5 mg once a year) on osteoporosis. Osteonecrosis of the jaw (ONJ) was observed in one patient in the placebo group and one in the treated group [21], with no significant difference between the two groups. The annual incidence of oral BP-treated BRONJ cases is 1.6–3.84/100,000 patients-treatment years according to data from Merck, and 0.7/100,000 patients-treatment years from the AAOMS [5]. Based on the occurrence of side effects and the results of a population-based study in Australia, the incidence of BRONJ was estimated to be 0.01–0.04% in patients treated with alendronate once per week and to increase to 0.09–0.34% after tooth extraction [18]. Another study in Germany reported an incidence of 0.00038% (3 cases in 780,000 persons) [22]. Taken together, these studies consistently show that the incidence of BRONJ in patients with osteoporosis is very low.

Estimated incidence in Japan

The precise incidence of BRONJ in Japan is unknown. A total of 35 cases of BRONJ in patients treated with oral alendronate for osteoporosis were reported in the literature and in abstracts presented at regional meetings from September 2001 to July 2008. The number of osteoporosis patients in Japan is estimated to be 12,000,000. Assuming a treatment rate is 20%, the number of treated patients is about 2,400,000, with approximately 600,000 treated with alendronate. Therefore, the estimated incidence of BRONJ is 5.8 cases/100,000 patients for the whole period after the launch of alendronate in 2001; this gives an estimated annual incidence of 0.85/100,000 patients-treatment years, which is comparable to the reports from Merck and the AAOMS.

The Committee of Survey and Planning in the Japanese Society of Oral and Maxillofacial Surgeons (JSOMS) has recently made a nationwide survey for incidence of BP-related osteomyelitis/osteonecrosis of the jaw between April 2006 and June 2008 at 248 in-service training institutes in the country: 568 cases of apparent BP-related osteomyelitis/osteonecrosis were registered and 529 cases turned out to be osteonecrosis. Among them, 263 cases of which the clinical course can be tracked by record were evaluated as genuine BRONJ based on the diagnostic criteria proposed by AAOMS. These 263 cases were composed of 152 (57.8%) intravenous BP related, 104 (39.5%) oral BP related, and 7 both related. These results suggest that the ratio of oral BP-related BRONJ over whole cases was higher in Japan than in the United States and the European Union. Moreover, the actual incidence of oral BP-related BRONJ can be calculated to be approximately 0.01–0.02% in Japan (unpublished data).

There are no solid reports on the incidence of intravenous BP-related BRONJ cases in patients with malignant bone diseases in Japan. A report on side effects from the Ministry of Health, Labor and Welfare for the period 2006–2008 indicated 123 cases of zoledronic acid-related BRONJ (including 51 in 2008) and 65 cases of pamidronate-related BRONJ (6 in 2008). These results suggest an incidence of zoledronic acid-related BRONJ of approximately 0.15% in 2008. However, the actual incidence may be higher and could be around 1–2%.

Imaging of BRONJ

A diagnostic imaging technique for prediction of the onset of BRONJ before detection of clinical bone exposure has yet to be established [23]. However, on conventional radiographs (intraoral and panoramic radiographs), osteosclerosis at the periphery of the alveolar bone, thickening and diffuse sclerosis of lamina dura, and widening of the periodontal ligament space have been reported as early signs of BRONJ [24, 25]. Osteolysis in the jawbone is also an important finding. However, it can be cancer metastasis to the jawbone, especially in patients with a malignant tumor.

When exposed bone is clinically seen, oral infection may modify image views. Conventional radiographs generally show an ill-defined patchy radiolucency (osteolysis) or a mixture of radiolucent and radiopaque (osteosclerosis) areas [24–28]. Osteosclerosis and bone surface irregularity on panoramic radiographs are observed more clearly as BRONJ progresses (Fig. 3) [29]. With progression of pathological changes, sequestration can be occasionally observed. It is reported that a periosteal reaction is rarely seen [24], but some reports suggest that an extensive periosteal reaction is observed in advanced stages of BRONJ compared to ordinary supprative osteomyelitis of the mandible [27, 30].

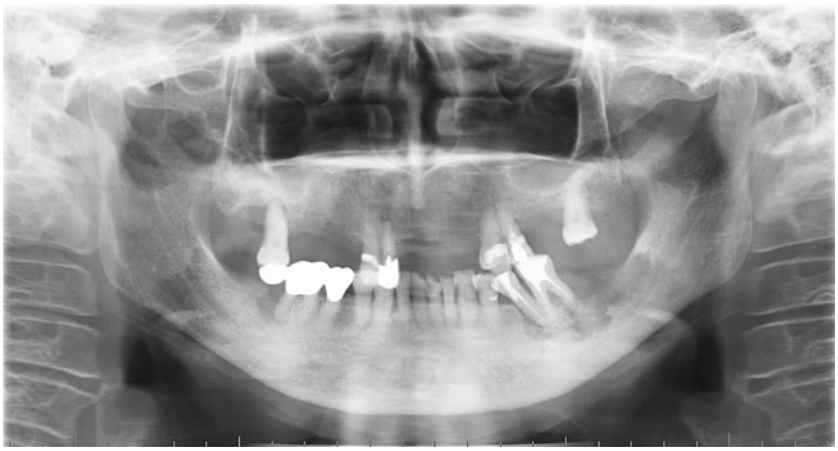

Fig. 3 Panoramic radiograph of BRONJ. A poorly defined patchy radiolucency (osteolysis) and radiopaque (osteosclerosis) area extend from the left mandibular molar region

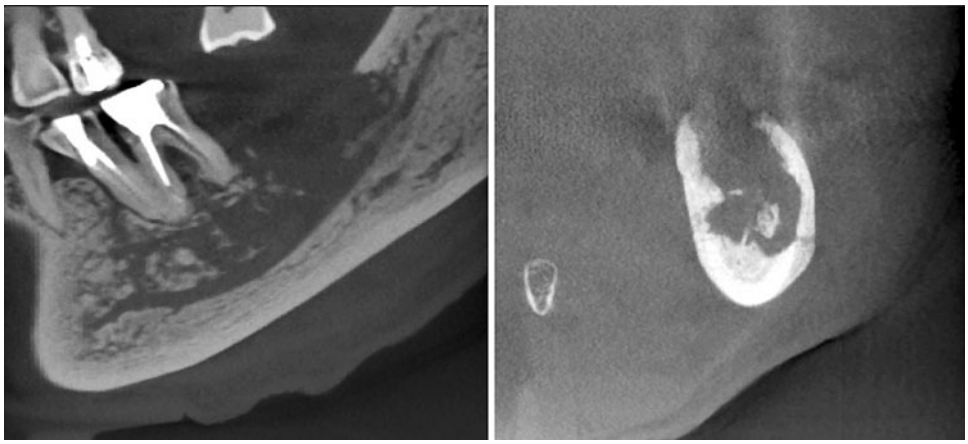

Fig. 4 Cone beam computed tomography of BRONJ. Discernible bucco-lingual cortical bone destruction can be seen, suggesting an advanced stage of illness

In addition to conventional radiography, computed tomography (CT) can reveal bucco-lingual cortical bone destruction more clearly at advanced stages of illness [26–28, 30–32] (Fig. 4). However, at present a CT view fails to allow us to predict the onset of BRONJ before to bone exposure.

Although the clinical presence of bone exposure longer than 8 weeks is an unanimous definition of BRONJ, there are some cases with no bone exposure but with symptoms such as internal dental fistula, external dental fistula, and an abnormal sensation (Vincent's symptom) and progressive osteolysis on radiographs. In these cases BRONJ can be suspected after exclusion of cancer metastasis to the jawbone. In support of this notion, Mawardi et al. [33] proposed the "Stage 0" concept, a potential stage of BRONJ before development of the clinically defined BRONJ. These authors suggest that presence of a sinus tract, a deep local periodontal pocket, or a longstanding unhealed tooth extraction wound may lead to bone exposure. In such cases, a mixture of patchy radiolucent and radiopaque areas or sequestrum may be seen on conventional radiographs.

Magnetic resonance imaging (MRI) of BRONJ typically shows low signal intensity in T_1-weighted images and medium to high signal intensity in T_2-weighted images or short T_I inversion recovery (STIR) images [28, 34], and high signal intensity in contrast-enhanced T_1-weighted images. However, one report indicated that both T_1- and T_2-weighted imaging gave low signal intensity [31]. Generally, T_1- and T_2-weighted images and STIR show low signals in osteonecrotic areas, which suggests a decrease in cells and blood vessel components [30–32, 34]. Both T_1- and T_2-weighted images show low signal intensity in the chronic stage, which reflect fibrosis or osteosclerosis. However, these findings do not necessarily represent specific characteristics of BRONJ [30, 32]. In the advanced stage, the periphery of the necrotic bone is surrounded by osteomyelitic bone, for which T_1-weighted images show low signal intensity and T_2-weighted images and STIR images show high signal intensity. These signals indicate increased cellular components, osteogenesis, and vascular proliferation [30, 32]. Importantly, there is a report that a lesion that is clinically undetectable can be detected by MRI [34], suggesting that MRI is useful for diagnosis of

early-stage BRONJ and that diagnostic imaging findings should be included in the definition of BRONJ.

Bone scintigraphy with ^{99m}Tc-disphosphonate (^{99m}Tc-MDP) may also be useful for detection of early changes in BRONJ [28, 32, 35]. O'Ryan et al. [36] observed positive tracer uptake in 66% of patients who underwent bone scintigraphy before clinical onset of BRONJ. However, whether bone scintigraphy can represent the clinical conditions of BRONJ has not been investigated. Low image resolution and less ability to identify osteonecrosis in the inflammatory region remain problematic.

Positron-emission tomography (PET) may also be a useful diagnostic modality, but it has the same problems as those of bone scintigraphy [26, 32, 37].

Krishnan et al. [38] have recently reported that they observed the widening of periodontal ligament space and osteosclerosis on CT, low signal intensity in the bone marrow on T_1-weighted MR imaging, and positive tracer uptake on bone scintigraphy before the onset of symptoms such as pain. These results imply the possibility that the combination of several imaging modalities may be more useful for early detection of BRONJ.

Histopathological view of BRONJ

Histopathological examination of BRONJ has been conducted using the orally exposed jawbones. The major characteristic findings are [30, 39, 40] (1) osteomyelitis containing necrotic bones and granulation tissues with inflammatory cells infiltration; (2) bacterial clusters of *Actinomyces* adjacent to necrotic bone (Fig. 5); and (3) pseudoepitheliomatous hyperplasia in the periphery of the necrotic bone.

1. It is unclear whether the osteomyelitis is caused by an infection secondary to the presence of BP-induced necrotic bones or a primary infection that subsequently induces necrotic bones [40–42].
2. Because *Actinomyces* is a resident oral bacterium frequently detected in refractory chronic osteomyelitis caused by opportunistic infection, BRONJ lesions appear homologous to refractory chronic osteomyelitis.
3. Pseudoepitheliomatous hyperplasia may allow resident oral bacteria such as *Actinomyces* to deeply invade into the jawbones [43].
4. Other notable histological findings of BRONJ lesions are that the number of osteoclasts either increases [44] or decreases [30] or that osteoclasts are seen apart from bone [45].

Histological and histomorphometric examination of wide areas of jawbones in BRONJ patients [46] indicates that there are three types of lesions in the jawbones of BRONJ patients: (1) lesions with acute inflammation, (2) lesions with osteonecrosis, and (3) no inflammation. The noninflammatory lesions show an increased bone mass as a consequence of the widening of trabecular bones and new bone formation in osteons compared to normal bones. However, the size and number of Haversian canals are reduced, suggesting that the blood supply is reduced in BRONJ jawbones, thus leading to necrosis and super infection. Of interest, osteoclast number was increased only in the osteonecrotic lesions.

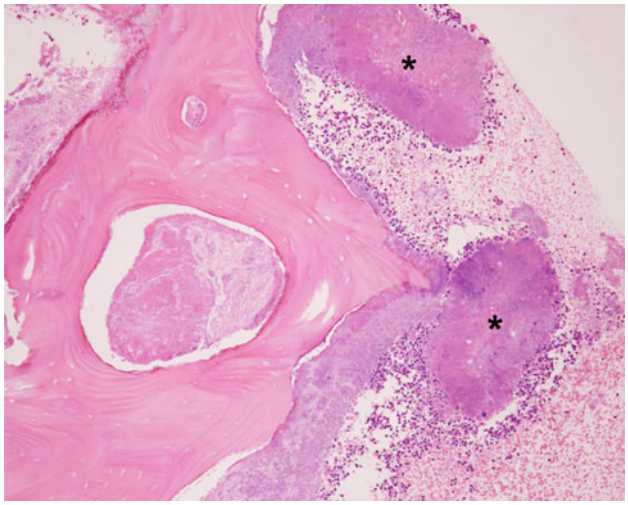

Fig. 5 Histopathological view of BRONJ. There is necrotic bone with no osteocytes in the lacunae (empty lacunae) and no cellular components in the bone marrow cavity. There are also two *Actinomyces* colonies (*asterisks*). [The authors are grateful to Dr. R. Kitamura (Department of Dentistry and Oral and Maxillofacial Surgery, Kansai Rosai Hospital, Amagasaki, Japan) and Dr. Y. Hoshida (Department of Pathology, Kansai Rosai Hospital, Amagasaki, Japan; present address: Department of Pathology, Sumitomo Hospital, Nakanoshima, Japan) for generously providing us with this histological picture]

Histopathological findings of radiation-induced osteonecrosis were compared with BRONJ. Hansen et al. [44] reported that radiation induced uniform necrosis over a wide range of the jawbone, whereas BRONJ demonstrates mosaic-like necrotic bones present in normal bones.

It has been proposed that ischemia caused by inhibition of angiogenesis by BPs [42, 47] is one of the mechanisms of BRONJ [48, 49]. However, several histopathological studies showed no significant inhibition of angiogenesis in the affected area and no relationship between inhibition of angiogenesis and onset of BRONJ [30, 39]. On the other hand, as shown by histomorphometric study of the jawbones in BRONJ patients reported by Favio et al. [46], it is reasonable to suggest that ischemia resulting from a decrease in blood supply to the jawbone is associated with BRONJ.

Using scanning electron microscopy, Hoefert et al. [50] examined bones obtained from patients with BRONJ,

osteomyelitis, radiation osteonecrosis, osteoporosis treated with BP but no BRONJ, and osteoporosis but untreated with a BP. They found a significant increase in microfractures in the bones from BRONJ. BRONJ only with microfractures was designated as "asymptomatic BRONJ" whereas BRONJ with microfractures together with bacterial invasion, jawbone infection, exposed bone, sinus tract, and pain were defined as "symptomatic BRONJ." This proposal is intriguing because recent studies suggest an involvement of osteocytes, which show apoptosis in BRONJ, in sensing microfractures [51].

In summary, diagnostic histopathological characteristics of BRONJ have yet to be established. In particular, as to whether osteomyelitis is the result of an infection caused by BP-induced osteonecrosis or osteonecrosis occurs secondary to BP-induced osteomyelitis needs to be clarified.

BRONJ and bone metabolic markers

BRONJ can be diagnosed based on treatment history with BPs, macroscopic findings for oral lesions, and radiographic imaging. Diagnosis of BRONJ is not difficult for dentists but may not be easy for physicians. As one of the likely causes of BRONJ is disturbed bone remodeling caused by an inhibition of osteoclastic bone resorption, the levels of bone resorption and bone formation markers in blood or urine may change with progression of BRONJ. Measurement of these biochemical markers may be useful for prediction of onset, diagnosis, follow-up of clinical course, and monitoring of therapeutic effectiveness, leading to an establishment of more effective therapeutic interventions for BRONJ [52]. Marx et al. [3] investigated the relationship between the blood levels of C-telopeptide (CTx), a marker for osteoclastic bone resorption, and the period of discontinuation of BP administration. These authors found that an elevation of blood CTx levels greater than 150 pg/ml following BP discontinuation was associated with recovery of osteoclastic bone resorption and that surgical dental treatments under these conditions did not cause BRONJ. These results led them to propose that the blood CTx concentration is a predictive marker for BRONJ. However, other reports did not support these results [53], with one report showing that bone metabolic markers in BRONJ patients were normal [54]. Overall, currently available evidence suggests that there is no significant relationship between bone metabolic markers and progression of BRONJ [55].

Risk factors for BRONJ

Risk factors for BRONJ can be categorized into five groups: (1) BP formulation, (2) local, (3) systemic, (4) genetic, and (5) others.

BP formulation

Zoledronic acid, which is used for the treatment of bone metastasis and hypercalcemia in cancer patients, gives the highest incidence of BRONJ. There have been few reports of BRONJ associated with BPs containing no nitrogen (etidronate and clodronate), whereas nitrogen-containing BPs (zoledronic acid, alendronate, risedronate, and pamidronate) show a strong relationship with BRONJ. These nitrogen-containing BPs have a high affinity for hydroxyapatite and a strong bone resorption inhibitory action, which may be a reason for the high incidence of BRONJ associated with those BPs. Furthermore, the incidence induced by a parenteral BP formulation is higher than that induced by an oral formulation, possibly because of the low absorption (<1%) of an oral formulation. The incidence of BRONJ also increases with dose, dosing frequency, and dosing duration. It has been reported that the incidence of BRONJ begins to increase approximately 1 year after intravenous zoledronic acid treatment and 2–3 years after oral BP administration [3, 18].

Local risk factors

Tooth extraction, dental implants, apical surgery, and periodontal surgery with invasion of the bone may be risk factors for BRONJ. These surgical dental procedures increase the incidence of BRONJ by more than sevenfold [56]. Inflammatory conditions such as periodontal diseases and periodontal abscess can also be risk factors. The incidence in the lower jaw is twice as high as that in the upper jaw, and regions where the gum is thin (mandibular torus, mylohyoid ridge, and palatal torus) are predilection sites for BRONJ [57, 58].

BRONJ and dental implants

The incidence of BRONJ is generally thought to increase with dental implants. However, Jeffcoat [59] reported that dental implants in 25 patients treated with alendronate caused no BRONJ in a 3-year prospective clinical study; also, no BRONJ occurred in patients treated with a placebo. Other studies have also shown that dental implants caused no cases of BRONJ [60, 61]. Thorough oral cleaning conducted before dental implants may make BRONJ less likely to develop. However, dental implants should still be considered as a risk factor, because the case numbers studied in a prospective study are too small and other studies are retrospective. An explanation of risks, benefits, and other prosthetic options should be given to patients in obtaining informed consent before dental implants.

Systemic risk factors

Because the majority of patients with cancers are receiving anticancer drugs, steroids, or radiotherapy, which disrupt immune functions, the risk of developing BRONJ is elevated in these patients. In addition, these cancer patients also are frequently administered larger doses of BP for the treatment of skeletal complications including bone metastasis, bone pain, and hypercalcemia than are osteoporosis patients. Consequently, the incidence of BRONJ could increase in these cancer patients. Similarly, patients with a history of Paget's disease of bone have a high incidence of BRONJ. Diabetes may also increase the incidence of BRONJ [62] (Table 4). Obesity is also a risk factor, although the mechanism is unknown [63]. In contrast, asthma, dyslipidemia, hypertension, and venous thrombosis may not be risk factors. Osteoporosis itself may be or may not be a risk factor.

Genetic risk factors

It will be of interest to determine whether genetic factors are associated with development of BRONJ. Matrix metalloproteinase-2 (MMP-2) [64] and polymorphisms of cytochrome P450 *CYP2C8* [65] have been suggested as genetic risk factors. It is noted that CYP2C8 is involved in arachidonic acid metabolism and cholesterol biosynthesis and may modulate angiogenesis and osteoblast differentiation in bone.

Other risk factors

Drugs such as cyclophosphamide, erythropoietin, and thalidomide are also listed as risk factors. Smoking and alcohol not only increase the incidence but also exacerbate the conditions. Poor oral hygiene is also a risk factor [66–70].

Table 4 Risk factors for BRONJ

Factor	Risk
Alcohol abuse	+
Asthma	–
Diabetes	2+
Hypercholesterolemia	–
Hypertension	–
Obesity	2+
Deep vein thrombosis	–
Osteoporosis	–
Anticancer therapy	+
Steroid therapy	+
Poor oral health	+
Smoking	2+

Modified from Khamaisi et al. [62]

BRONJ and periodontal diseases

Periodontal disease is an infection caused by oral bacterial infiltration in the periodontal pockets between the teeth and gingiva. It initiates with gingivitis, followed by spreading to all the periodontal tissues to cause periodontitis. The teeth are loosened by alveolar bone resorption, finally resulting in tooth loss. Individual differences in host defense are strongly related to the onset and progression of periodontal disease. Patients with diabetes or human immunodeficiency virus (HIV) infection whose immunity is decreased are particularly susceptible to the disease. Patients with postmenopausal osteoporosis are also at risk for periodontal diseases.

Periodontal diseases are observed in 84% of BRONJ patients [58]. Oral bacteria and periodontal diseases are critical risk factors for BRONJ. Tooth extraction and periodontal surgery (e.g., flap operation) are major risk factors, although root planing and curettage of the dental pocket in primary periodontal treatment are minor risk factors for BRONJ. Removal of bacteria in the oral cavity before BP administration is important for prevention of BRONJ. Therefore, patients treated with BP, especially intravenous BPs, are advised to undergo oral examinations, screening for periodontal diseases (including radiography), and oral cleaning by a dental hygienist before BP administration. When there is an indication of tooth extraction, teeth affected with periodontal disease should be removed before BP administration. BP treatment should be started only after observing the primary healing of the extraction sockets 2 or 3 weeks after extraction. Mild periodontitis without an infrabony pocket is not a major problem for primary periodontal treatment regardless of use of intravenous or oral BPs. However, moderate or severe periodontitis with an infrabony pocket requires extensive care even in primary periodontal treatment. For example, invasive pocket curettage should be avoided as much as possible. Tooth extraction in severe periodontitis should be performed before BP administration. Periodontal surgery such as a flap operation is contraindicated for patients receiving BP. These patients should be instructed in oral cleaning by an oral hygienist every 1 or 2 months during BP administration.

In summary:

1. Patients scheduled for BP treatment should undergo oral examination by a dentist before BP administration. In particular, patients who will receive parenteral BPs should be examined for periodontal diseases (including radiography), and dental treatments should be conducted on a priority basis [58, 71, 72].
2. Before dental treatments, thorough oral cleaning is essential. Oral care should be conducted by a dental

hygienist in parallel with dental treatments [58, 69, 71, 72]. Cessation of smoking and restriction of alcohol intake are also required [72].

3. For oral treatments for BRONJ patients, alleviation of acute symptoms, including pain (regional cleaning, antibacterial gargle, etc.), should first be conducted, followed by prevention of secondary infection (administration of antibacterial drugs) and removal of necrotic tissues. Conservative procedures are desirable, and unnecessary aggressive curettage is contraindicated [72–74].

Factors potentially involved in the pathogenesis of BRONJ

It is yet unproved that BPs truly cause ONJ. However, several potential mechanisms can be proposed based on currently known actions of BPs.

Suppression of osteoclastic bone resorption

Nitrogen-containing BPs induce apoptosis in bone-resorbing osteoclasts via the mevalonate pathway, leading to an inhibition of bone resorption and consequent suppression of bone remodeling. Decreased bone remodeling could be one of the causes of BRONJ. Active bone remodeling is essential for healing of a tooth extraction wound, and inhibition of bone remodeling by BP delays the healing process and increases the chances of oral bacterial infection. In addition, BP treatment also inhibits removal of the necrotic bones by osteoclasts.

Suppression of osteocytes

Histological examination clearly shows that the bones affected with BRONJ have very few osteocytes in the lacunae. Intrinsically, osteocytes undergo spontaneous cell death, and suppression of bone remodeling increases the number of dead osteocytes [75]. Therefore, BP-induced suppression of bone remodeling caused by inhibition of osteoclastic bone resorption may increase the number of dead osteocytes in the lacunae and cause progression of BRONJ.

Involvement of oral bacteria

There are almost 800 types of bacteria (10^{11}–10^{12}/cm^3) in the human oral cavity, which is comparable to the number of bacteria in feces. Histological examination [43] by conventional and scanning electron microscopy [76] shows marked proliferation of resident oral bacteria such as *Actinomyces* in the necrotic jawbones. A recent in vitro study describes that high concentrations of BP (10^{-4}–10^{-3} M) promote proliferation of oral bacteria. Adherence of oral bacterium to BP-containing bone is increased compared to control bone. These results suggest that BP may increase biofilm formation on tooth surface (dental plaque) [77]. These results suggest an involvement of oral bacteria in the development of BRONJ, which could be the reason why BRONJ develops only in the jawbones.

Inhibition of angiogenesis, vasculature, and blood flow

Femoral head necrosis is a pathological change representing necrosis of bone. The etiology of femoral head necrosis includes an insufficient blood supply with no bacterial infection. Blood supply insufficiency may be also related to BRONJ. Zoledronic acid, which is associated with the highest incidence of BRONJ, has strong inhibitory effects on angiogenesis [78]. Angiogenesis is essential for healing of tooth extraction wounds, and inhibition of angiogenesis delays the healing process. BP may cause the obstruction of intraosseous blood vessels and necrosis of osteocytes around these blood vessels [43], which in turn may induce BRONJ. Along this line, it is noted that ONJ also develops in cancer patients treated with bevacizumab, which is a human recombinant neutralizing antibody for vascular endothelial growth factor (VEGF) and a potent inhibitor of angiogenesis [79]. These reports suggest that inhibition of angiogenesis is associated with the development of BRONJ. Blood flow into the tissue is known to be correlated with the metabolic activity of the tissue [75]. Decreased blood flow to the jawbones caused by BP treatment may thus reduce the metabolic activity of the jawbones and may eventually cause BRONJ.

On the other hand, several studies found no significant inhibition of angiogenesis in the affected area and no relationship of inhibition of angiogenesis with onset of BRONJ [30, 39]. Further studies are needed to define the role of angiogenesis in the pathogenesis of BRONJ.

Inhibition of proliferation and migration of epithelial cells

A tooth extraction wound is closed through proliferation and migration of oral epithelial cells. A recent study has reported that BP inhibits migration and proliferation of oral epithelial cells but not fibroblasts [77]. Inhibition of proliferation and migration of oral epithelial cells by BP leaking from alveolar bone following a tooth extraction may thus cause a delay in socket closure and leave the

socket open[80–82], thereby increasing the risk of oral bacterial infection.

Osteosclerosis

Accumulation of BP makes alveolar bone sclerotic and thereby extraction more difficult and traumatic [77], presumably leaving larger wounds that consequently require a longer healing time.

Immune dysfunction

Immune function may generally be impaired in aged patients and cancer patients treated with anticancer drugs and/or steroids. Infection may increase in these patients.

A summary of the hypothetical mechanism of BRONJ is illustrated in Fig. 6.

Animal models of BRONJ

Establishment of an animal model that resembles clinical conditions of BRONJ in human is important to examine the mechanism of BRONJ and subsequently design new therapeutic interventions. It has been shown that 3-year oral BP administration induces necrosis in the bone matrix of the mandible in beagle dogs [83], and that tooth extraction in rats pretreated with BP and steroids produces jawbone lesions resembling BRONJ in patients [84]. However, because these models failed to be accompanied with bacterial infection as observed in human BRONJ, their usefulness is yet to be determined. Establishment of better animal models is awaited.

BP administration and dental treatments

Patients scheduled to receive a parenteral BP for treatment of malignant bone diseases

For patients scheduled to receive parenteral BP formulation, an oral examination should be extensively performed to check for risk factors for BRONJ. The patients should also be informed of the importance of maintaining good oral hygiene through education and instruction by dentists or dental hygienists. Additionally, preventive dental treatments should be conducted if needed. For patients with dentures, the gingival condition should be evaluated by examining the posterior gum on the lingual side of the lower jaw. If possible, administration of the BP should be initiated only after completion of dental treatments and improvement of the oral condition [85, 86]. If this is difficult, dental treatments should be conducted in parallel with BP administration but before the BP dose reaches a high level.

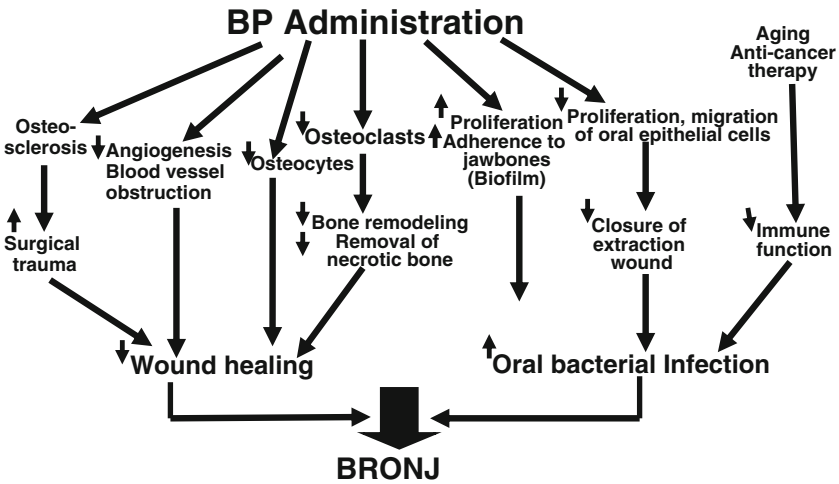

Fig. 6 Hypothetical mechanisms of BRONJ. Bisphosphonates (BP) induce apoptosis in osteoclasts and inhibit bone resorption and consequent bone remodeling. BP treatment also inhibits removal of the inflammatory necrotic bones by osteoclasts, which leads to a delay in wound healing and an increase in chances of oral bacterial infection. Bones affected with BRONJ have very few osteocytes in the lacunae. BP may increase the number of dead osteocytes in the lacunae and cause progression of BRONJ. BP may increase biofilm formation on tooth surface by promoting proliferation and adherence of oral bacteria, which could be the reason BRONJ develops only in the jawbones. BP may delay wound healing by inhibiting angiogenesis. BP may cause obstruction of intraosseous blood vessels and necrosis of osteocytes around these blood vessels. BP inhibits migration and proliferation of oral epithelial cells, causing a delay in socket closure that leaves the socket open, thereby increasing the risk of oral bacterial infection. Accumulation of BP makes alveolar bone sclerotic and thereby extraction is more difficult and traumatic, leaving larger wounds that consequently require a longer healing time. Immune function is impaired in aged patients and in cancer patients treated with anticancer drugs and/or steroids. Infection may increase in these patients

Patients receiving an intravenous BP for treatment of malignant bone diseases

Maintenance of good oral hygiene is important through education and instruction of patients receiving parenteral BP, such that dental treatments can be avoided as much as possible. If dental treatments are desperately required, nonsurgical treatments are suggested rather than surgical treatments such as tooth extraction or dental implants.

Discontinuation of an intravenous BP administration (drug holiday)

Discontinuation of BP administration (drug holiday) before dental treatments is a controversial issue. BP remains bound to bone hydroxyapatites for almost 10 years [87]. Zoledronic acid has been shown to increase the bone mineral density of the lumbar spine by 2.7% over 1 year and by 4.3% over 3 years after a single injection, showing that BP deposited in the bone has long-term sustained action. Therefore, even if administration of BP is discontinued for a short period of time before a surgical dental procedure, the effects of this practice on prevention of BRONJ are questionable. In fact, it should be noted that at the moment there is no concrete evidence that a drug holiday from BP reduces the incidence of BRONJ. Because almost all the patients treated with parenteral BPs have cancer, BP administration often cannot be discontinued for the management of skeletal-related events such as bone metastasis, hypercalcemia, bone pain, paresis, and pathological fractures. Thus, in principle, dental treatments are conducted without discontinuation of BP administration in these cancer patients. However, if possible, it would be desirable that BP be discontinued for 2–3 months before dental treatment under these circumstances. In any case, however, a full explanation of BRONJ risk to the patients and acquisition of informed consent from the patients are essential. Physicians and dentists should collaborate to give preventive treatments such as preoperative removal of dental plaque and use of antibacterial drugs and oral cleaning agents and prepare for appropriate strategies including a consideration of legal issues in case BRONJ occurs.

Recently, the European Myeloma Network has proposed that BP treatment should be discontinued when BRONJ develops in patients with multiple myeloma and resumed when myeloma starts to progress again [88].

BRONJ and pediatric patients with osteogenesis imperfecta

Osteogenesis imperfecta (OI), caused by a type I collagen gene mutation, is a congenital disease with frequent fractures resulting from decreased bone mass and deteriorated bone quality [89]. Intravenous administration of pamidronate is effective for treatment of OI, but development of BRONJ is a concern when pediatric patients with OI undergo surgical dental treatments such as extraction of a primary tooth. However, to date no BRONJ case has been reported following surgical dental treatments in pediatric patients with OI [90–92]. Reasons for this are unclear. Children may have differences in bone metabolism, immune systems, or oral bacterial phenotype compared to those of adults.

Patients scheduled to receive BP treatment for osteoporosis

With appropriate dental treatments and maintenance of good oral hygiene, there is no need to delay BP administration for treatment of osteoporosis. Only routine examinations are required. However, to avoid tooth extraction and other surgical dental treatments during BP administration, patients should be instructed not to smoke or consume alcohol and to maintain good oral hygiene. If surgical dental treatments are inevitable, it would be desirable that BP administration is started after complete healing of the wound is verified.

Patients receiving BP treatment for osteoporosis

As the feasible way to prevent BRONJ is to maintain good oral hygiene and oral care through routine dental examinations, patient education and instruction are important. The incidence of BRONJ in patients treated with an oral BP is extremely low (<1/100,000). Therefore, the strict care paid cancer patients who are treated with parenteral BPs may not be necessary for patients receiving an oral BP. An intravenous formulation [once-yearly administration of Zometa (Aclast)] is sometimes used for treatment of osteoporosis in the United States and Europe but is yet to be approved in Japan. However, because the dose is much lower than that used for cancer patients, the risk for developing BRONJ appears to be small.

Discontinuation of an oral BP administration

Earlier reports show that the incidence of BRONJ increases in 2 [18] to 3 [58] years of oral BP administration. Thus, 3 years is a critical administration period that significantly influences the following management of patients receiving oral BP. The presence of systemic or local risk factors may be also significantly influential. We therefore propose the following.

a. For patients who have been administered with oral BP for less than 3 years and have no evident risk factors, there is little need to postpone or avoid dental treatments or to discontinue oral BP administration.
b. For patients who have been administered with oral BP for longer than 3 years or have risk factors, the physicians who prescribed the BP and the dentists should closely discuss the increased risk for fracture after discontinuation of BP administration and the need for surgical dental treatments. The risk of developing BRONJ after surgical dental treatments should be extensively explained to the patients. If the patient wants to undergo dental treatments, informed consent must be obtained beforehand.
c. Curtis et al. [93] examined the rate of hip fracture among women aged between 60 and 78 years old compliant with BPs therapy for 2 years who subsequently discontinued and suggested that discontinuation is not advisable under these conditions, because the adjusted hazard ratio of hip fracture per 90 days following discontinuation of nitrogen-containing BPs was 1.2 (range, 1.1–1.3) and that the hazard ratio after more than 9 months discontinuation was 3.1 (range, 1.5–6.1). Thus, physicians need to explain the increase in risk of fracture related to discontinuation of BPs for these patients.
d. If fracture risk is minimal and BP administration can be discontinued, 3 months at least is required based on turnover rates of bone remodeling. One report has suggested that a longer discontinuation period of BP is associated with a greater reduction in the incidence of BRONJ [3].
e. To prevent postsurgical oral bacterial infection, dental plaques are thoroughly removed before dental treatment. Administration of antibacterial agents before, during, and after the treatments may be also effective. If possible, suture of the tooth extraction wound may also reduce postsurgical oral bacterial infection.

Readministration of an oral BP after tooth extraction

Because bone remodeling in extraction wounds is usually complete in 2 months, it is suggested that BP administration be avoided during this period. However, when earlier readministration of BP is required for the treatment of the primary disease, BP can be given 2 weeks after tooth extraction if the extraction wound shows primary healing with no evident sign of infection.

Therapeutic strategy for BRONJ

Therapeutic goals

The therapeutic goals in treatment of BRONJ are as follows:

1. To minimize progression of BRONJ.
2. To alleviate pain, abnormal sensation, and infection to maintain the quality of life (QOL) of patients.
3. To conduct frequent patient education and instruction and follow-up examinations to prevent relapse of BRONJ.

Treatment of BRONJ

BRONJ should be treated according to its severity.

1. Observational period (stage 0): No exposed bone/necrosis but an abnormal sensation in the mental region (Vincent's symptom), intraoral sinus tract, or a deep periodontal pocket. Plain radiography shows small osteolytic lesions.

Patient education on the symptoms and risk of BRONJ and maintenance of good oral hygiene through routine dental examinations and preventive care are important. Conservative treatments such as using oral antibacterial mouthwashes, cleaning the fistula or periodontal pocket, and local application and injection of antibacterial drugs should be performed with routine follow-up. Aggressive treatments are not required, and there is no indication for surgical treatment.

2. Stage 1: Exposed bone/necrosis but no symptoms. Plain radiography shows osteolytic lesions.

Treatments are basically identical to the observational period. Conservative treatments such as oral antibacterial mouthwashes, cleaning of exposed bone and necrotic regions, and application of antibacterial drugs should be performed with routine follow-up. There is no indication for surgical treatment.

3. Stage 2: Exposed bone/necrosis and inflammatory symptoms such as pain and purulent discharge. Plain radiography shows extensive osteolytic lesions.

Concomitant use of appropriate oral antibacterial mouthwashes and antibacterial drugs is effective after conducting bacterial culture tests and antibacterial sensitivity tests for the lesions [10, 15, 57, 94, 95]. Antibacterial drugs should be carefully selected if *Actinomyces* is isolated in bacterial culture. Combination, long-term, or continuous antibacterial therapy may be required for refractory patients. The Canadian Association of Oral and

Maxillofacial Surgeons proposes a 3-week course of continuous antibacterial therapy for Stage 2 [72].

4. Stage 3: In addition to the findings in stage 2, external dental fistulae and pathological fractures are observed. Plain radiography shows broad osteolysis extending to the inferior margin of the mandible.

Treatment is very difficult when BRONJ has progressed to this stage. The sequestra which may affect the soft tissues should be curetted, but only to a minimal extent without exposing normal bone. The separated sequestra should be removed without exposing normal bone. Exposed bones and teeth in the sequestra that are unlikely to exacerbate necrosis can be removed. A good nutritional condition should be maintained with supplements or transfusion in patients with stage 3 BRONJ because they may be at risk for malnutrition from disruption of oral intake.

Invasive dental treatments should be avoided whenever possible in patients with stage 3 BRONJ because they may increase the risk of development of additional exposed and necrotic bones. However, curettage or surgical removal of jawbones and antibacterial therapy may occasionally bring long-term alleviation of symptoms and resolution of acute infection and pain. Marginal or segmental resection of the mandible should be conducted in patients with pathological fractures of the mandible and those with large areas of sequestrum, which could be a continuous cause of infection that is not susceptible to mouthwashes or antibacterial drugs. The success rate of surgical resection is high in BRONJ associated with oral BP administration, although postsurgical prognosis is unclear in intravenous BP-related BRONJ [96]. In addition, immediate reconstruction with a plate or a musculocutaneous flap should be considered, with special care to avoid postsurgical infection [97]. In performing the surgery, it should be recognized that abnormal bone remodeling caused by BP treatment is likely to affect fixation of the reconstruction plates.

5. Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO), which has been developed to assist surgery and antibacterial drugs, is shown to efficiently enhance wound healing. HBO has been used for treatment of radiation necrosis or chronic osteomyelitis of the jawbone during the past 20 years [98]. A classical theory proposes that HBO accelerates healing by enhancing the ability of leukocytes to kill pathogens by increasing the oxygen concentration. A recent study also showed that HBO generates reactive oxygen species (ROS) and reactive nitrogen species (RNS) that activate intracellular signals which are important for wound healing [98]. Because one of the causes of BRONJ is inhibition of osteoclasts, of which differentiation, function, and lifetime are regulated by signaling molecules sensitive to reactive oxygen, HBO may have therapeutic effects on BRONJ. However, results for the effects of HBO on BRONJ vary, and the efficacy has yet to be determined.

6. Other therapeutic interventions

BRONJ may be improved by subcutaneous injection of recombinant parathyroid hormone-related protein (PTH-rP) (1–34) [99], and bortezomib, a proteasome inhibitor used in multiple myeloma, is also reported to be effective for BRONJ [100]. Further studies are needed to verify the therapeutic efficacy of these treatments.

Administration of BP in patients with BRONJ

1. Patients treated with a parenteral BP for malignant bone diseases

Cancer patients and patients at high risk for hypercalcemia, bone pain, or pathological fracture caused by a malignant tumor greatly benefit from treatment with a parenteral BP. Thus, discontinuation of a parenteral BP administration is often difficult in these cancer patients even when BRONJ occurs. Nevertheless, efforts in which BRONJ symptoms are alleviated to prevent progression or occurrence in other regions should be made from a long-term point of view. Regarding the impact of discontinuation of a parenteral BP on the healing process of BRONJ, it was reported that symptoms were improved in 7 of 60 patients who discontinued BP administration for 6 months or more [72]. However, another report indicated that BP discontinuation had no impact on the prognosis of BRONJ [101]. Treatment of the malignant disease should always be the priority in cancer patients receiving a parenteral BP formulation.

2. Patients treated with a BP for osteoporosis

When BRONJ occurs in patients with osteoporosis, temporary discontinuation of BP administration or a switch from BP to other drugs should be considered if there is little risk for fracture. In fact, discontinuation of an oral BP has been shown to be effective for spontaneous separation and discharge of the sequestrum or improvement of symptoms after curettage [3].

Team approach among physicians, dentists, and pharmacists

A team medical care system including physicians, dentists/oral surgeons, pharmacists, nurses, dental hygienists, and dental technicians is required to properly manage BRONJ. It is suggested that the following issues are managed in the management of BRONJ:

- Physicians are required to keep in mind the possibility of the development of BRONJ following BP treatment in patients with malignant bone diseases or osteoporosis. BP should be given in parallel with oral

cleaning in dental practice to reduce the risk of development of BRONJ. It is also desired that physicians understand the anatomy, physiology, and function of oral cavity and teeth and procedures and the significance of dental treatments, especially tooth extraction.

- Dentists understand the clinical conditions and symptoms of the primary disease in a patient, the drug efficacy and mechanism of action of BPs, and the incidence of BRONJ. They are also required to attempt, as much as possible, to perform nonsurgical conservative dental treatments without excessive unnecessary concerns regarding BRONJ development.
- Pharmacists are expected to explain to patients about the effectiveness of BPs at prevention of fractures due to osteoporosis, the very low incidence of BRONJ by oral BPs, and prevention of BRONJ by oral cleaning before to dental treatments.
- When invasive dental treatments are inevitable due to a request of a patient or to maintain QOL, the physicians should explain the clinical conditions of the primary disease and the risk of BRONJ to the patients. Meanwhile, the dentists/oral surgeons should explain the risk of development, clinical course, and prognosis of BRONJ to the patients. Dental treatments should be started only after obtaining informed consent from the patient. At the same time, the physicians and dentists/oral surgeons should discuss the discontinuation of BP administration and reach an agreement. In addition, the physicians and dentists should discuss how to manage BRONJ when it occurs.
- Once discontinuation of BP administration is decided, the physicians and dentists/oral surgeons should discuss the duration of discontinuation and timing of restart of BP administration before dental treatments and reach an agreement. In addition, the physicians should attempt to use an alternative route of administration, reduced dosage of BPs, or equivalent drugs for treatment of the primary disease.
- When discontinuation of BP administration is not possible, the physicians should explain the possibility of occurrence, clinical course, and prognosis of BRONJ after dental treatments to the patient. The dentists/oral surgeons should extensively conduct preventive treatments to reduce the risk of BRONJ such as preoperative oral cleaning before dental treatments and pre-, intra-, and postoperative administration of antibacterial drugs.
- Dentists should pay attention to avoidance of infection and of unnecessary surgical wounds during dental treatments.
- When BP administration is restarted, the physicians and dentists/oral surgeons should determine the timing by carefully observing the healing of the surgical wounds and considering the clinical condition of the primary disease.
- Because legal problems may arise between physicians/dentists and the patients from the occurrence of BRONJ, discussion to cope with this issue should be conducted beforehand.

Future perspectives

When BRONJ was first reported in 2003, the mechanism, clinical conditions, and management were almost totally unclear. Consequently, physicians and dentists had difficulties in taking appropriate actions. The mechanism (especially direct involvement of BPs) of BRONJ is still not fully understood. However, accumulated case reports of BRONJ have to some extent revealed the pathophysiology, clinical conditions, and appropriate therapeutic interventions. In particular, the incidence of BRONJ after surgical dental treatments is significantly decreased by conducting patient education on the importance of oral cleaning and performing thorough oral cleaning and pretreatment with antibacterial drugs. A close relationship between oral bacterial infection and development of BRONJ has been also suggested. Physicians now carefully plan BP administration with consideration of the risk of BRONJ. It is expected that the accumulating information and experience obtained from many clinical cases will lead to a significant reduction of serious BRONJ cases in the future.

Since the first report by Marx in 2003 [49], the term "necrosis" has been used. However, because the main causes of BRONJ are likely infection and immune dysfunction, "osteomyelitis" may be more appropriate for describing this disease [102]. Furthermore, patients may be less afraid of a term such as "inflammation," rather than "necrosis," when used in an explanation of BRONJ. Thus, we would like to propose that this disease is more appropriately referred to as "chronic osteomyelitis of the jaw" rather than "necrosis of the jaw."

More recently, Taylor et al. [103] published a case report in which anti-RANKL (receptor activator of nuclear factor-kappaB ligand) antibody denosumab, a potent inhibitor of osteoclastic bone resorption with a different mechanism of action from BP, caused ONJ in cancer patients. Similarly, it was reported that denosumab induced ONJ at an equal frequency to zoledronic acid (*European Journal of Cancer Supplements* 7:11 Abstract # 20 LBA 2009; Amgen press release, 3 August 2009). These results collectively suggest that suppression of osteoclastic bone resorption is critical in the pathogenesis of BRONJ and that BP itself may not be responsible for ONJ. If this turns out to be the case, any type of antiosteoclastic agents can be

associated with ONJ and thus must be administered with caution. Furthermore, our preventative or therapeutic approaches for BRONJ may need to be reconsidered.

Last, we would like to note that this position paper does not describe the results of systematic prospective clinical studies and was not written based on basic experimental data but on a summary of experiences, observations, and assumptions made in published BRONJ cases in the literature. Therefore, it is suggested that readers remember that this article is not the result of evidence-based medicine.

Appendix

Toshiyuki Yoneda, Hiroshi Hagino, Toshitsugu Sugimoto, Shunji Takahashi: The Japanese Society for Bone and Mineral Research; Hiroaki Ohta, Satoshi Soen, Satoru Toyosawa: Japan Osteoporosis Society; Akira Taguchi: The Japanese Society for Oral and Maxillofacial Radiology; Toshihiko Nagata: The Japanese Society of Periodontology; Masahiro Urade: The Japanese Society of Oral and Maxillofacial Surgeons.

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