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Review Article

Novel insight into the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ)☆

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SUMMARY

Bisphosphonate-related osteonecrosis of the jaw (BRONJ), characterized by refractory bone exposure, has recently emerged as a serious side effect of bisphosphonate (BPs) treatment. We discuss novel insights that may help to improve the efficacy of BRONJ treatment and prevention. Our report highlights the following: (1) The presence of exposed bone in patients taking BPs does not necessarily reflect BRONJ, and diagnoses of oral ulceration with bone sequestration and malignancy must be excluded. (2) Osteonecrosis type of BRONJ is difficult to avoid using preventive dental measures alone. However, as with osteomyelitis type of BRONJ, preventive dental measures are indispensable for reducing the risk of secondary infection and disease progression. (3) The importance of tooth extraction as a risk factor for BRONJ among patients taking BPs has been overstated, particularly when they are administered at low doses. Delaying tooth extraction may increase the risk for the onset and progression of osteomyelitic BRONJ. (4) In patients taking low doses of BPs, dental implant surgery is not necessarily contraindicated if there are no other risk factors, such as combined use of corticosteroids or concomitant diabetes. However, the risk of BRONJ due to peri-implantitis must be explained when obtaining patient consent.

1. Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ), which is characterized by refractory bone exposure, has recently emerged as a serious side effect of bisphosphonate (BPs) treatment (Fig. 1). BRONJ was first thought to be due to administration of high doses of intravenous BPs to treat metastatic bone lesions or multiple myeloma. However, more recent studies have indicated that BRONJ also frequently occurs in patients receiving low doses of oral BPs for the treatment of osteoporosis [1,2]. In addition, patients treated with denosumab – a human monoclonal antibody against receptor activator of nuclear factor-kappa B ligand (RANKL) whose antiresorptive effects differ from those of BPs – may develop denosumab-related osteonecrosis of the jaw (DRONJ). DRONJ is clinically indistinguishable from BRONJ and occurs at almost the same rate [3].

Although the pathophysiology of BRONJ remains unclear and the number of affected patients is increasing in Japan, significant improvements have been made with respect to risk reduction strategies and treatment. In the present report, we discuss novel insights that may help to improve the efficacy of BRONJ treatment and prevention, as data are far more abundant for BRONJ than for DRONJ.

2. Recent evidence

Since a 2003 report by Marx [4], in which the author described a case of avascular necrosis of the jaw in a patient treated with pamidronate (Aredia) and zoledronate (Zometa), numerous cases of BRONJ have been reported worldwide, including in Japan. These reports have indicated (1) that the incidence of BRONJ is increasing in Japan, (2) that osteonecrosis of the jaw (ONJ) may also be caused by drugs other than BPs, and (3) that some cases of BRONJ are curable or preventable.

2.1. Epidemiology of BRONJ in Japan

The 2017 position paper on antiresorptive agent-related osteonecrosis of the jaw (ARONJ) (PP 2017) was compiled by the Japanese Allied Committee on Osteonecrosis of the Jaw [1]. The committee was organized through a collaboration among six academic societies: the Japanese Society for Bone and Mineral Research, the Japan Osteoporosis Society, the Japanese Society of

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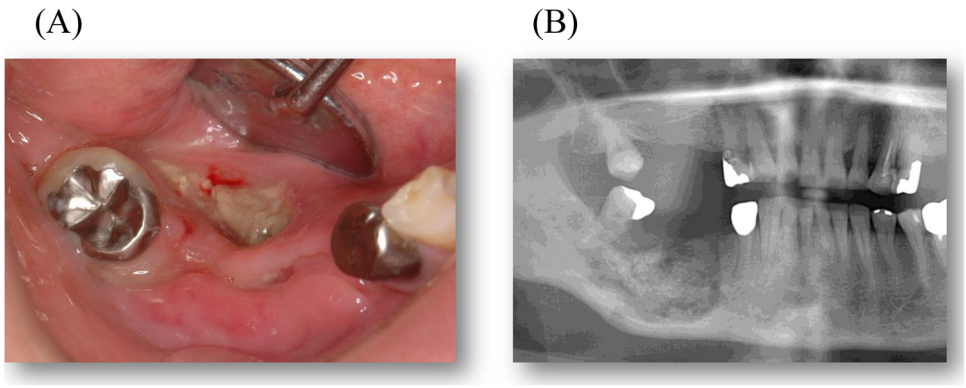

Figure 1. (A) Typical BRONJ with exposure of the jawbone. (B) Orthopantomogram showing separation of the sequestrum.
BRONJ: bisphosphonate-related osteonecrosis of the jaw.

Periodontology, the Japanese Society of Oral and Maxillofacial Radiology, the Japanese Society of Oral and Maxillofacial Surgeons, and the Japanese Society of Clinical Oral Pathology.

The Japanese Society of Oral and Maxillofacial Surgeons identified 263 cases of BRONJ between 2006 and 2008 [5]. However, a total of 4797 cases were identified between 2011 and 2013 [6], representing a nearly 20-fold increase in the incidence of BRONJ, based on data from two nationwide surveys. Approximately 40% of patients with BRONJ in the 2006–2008 group and half of those in the 2011–2013 group developed BRONJ following treatment with oral BPs [1]. These results in Japan differ from those obtained in other countries, which have reported a higher incidence of BRONJ in patients treated with intravenous (high dose) versus oral (low dose) BPs.

According to the consensus report published by the International Task Force on Osteonecrosis of the Jaw [2], the incidence of BRONJ in patients with osteoporosis treated with low-dose oral BPs ranges from 1.04 to 69 per 100,000 patient-years. In patients with bone cancer treated with high-dose intravenous BPs, the incidence of BRONJ ranges from 0 to 12,222 per 100,000 patient-years [2]. Despite the publication of the first position paper on BRONJ in Japan in 2010 [7], such increases in incidence are hypothesized to result from increases in the long-term use of BPs. Previous findings have suggested that inadequate preventive measures may be responsible for increases in BRONJ incidence, and that physicians in Japan display an inadequate understanding or interest in dental treatment (PP 2017) [1].

2.2. ONJ associated with medications other than BPs

Although ONJ can be caused by BPs treatment, research has indicated that other medications may also cause ONJ. Such medications include the antiresorptive agent denosumab, the anti-angiogenic vascular endothelial growth factor (VEGF) inhibitor bevacizumab, and the tyrosine kinase inhibitor sunitinib. Due to these findings, the American Association of Oral and Maxillofacial Surgeons (AAOMS) revised the nomenclature to medication-related osteonecrosis of the jaw (MRONJ) in their 2014 position paper (AAOMS 2014) [8].

While BPs, denosumab, bevacizumab, and sunitinib were identified as causative agents of MRONJ in the AAOMS 2014 report, additional studies have indicated that ONJ can be caused by single agent of corticosteroids [9,10], methotrexate [11,12], and recreational or illicit drugs such as cocaine, amphetamine, and methamphetamine [13,14]. Because corticosteroids and methotrexate are also commonly used in conjunction with BPs or denosumab, it is important to check an accurate medical past history and history of drug use for all patients.

As indicated by the International Task Force on ONJ, some pathological bone exposure and osteonecrosis are unrelated to medication use which is called oral ulceration and benign sequestration (or oral ulceration with bone sequestration) (OUBS) [2,15]. Although OUBS is difficult to define, typical cases are triggered by trauma or aphtha near the mandibular mylohyoid line, with conservative treatment resulting in healing following spontaneous detachment of necrotic bone after several months. Because some cases of OUBS heal spontaneously, they may go unnoticed by both patients and healthcare professionals. Thus, the incidence of OUBS remains unknown, and few cases of OUBS have been reported in patients who have taken medications such as antiresorptive agents. It is therefore difficult to determine whether a patient with bone exposure who has used antiresorptive agents should be diagnosed with OUBS or ARONJ. Due to the rarity of the condition, patients with OUBS may be misdiagnosed with stage 1 ARONJ.

2.3. Treatment of BRONJ

Previously, BRONJ was difficult to cure, and nonsurgical treatment options such as local irrigation were common. Surgical modalities range from conservative (e.g., debridement, bone curettage, and sequestrectomy) to radical (e.g., marginal/segmental resection), and increasing evidence suggests that surgical treatment is more effective than non-surgical treatment. The surgical resection of necrotic jawbone has traditionally been considered palliative rather than curative, as it has been offered primarily to patients with advanced disease who have not responded to nonsurgical treatment [16]. There is now enough evidence to suggest that nonsurgical treatment often fails to provide positive outcomes in patients with advanced BRONJ [16,17], whereas radical surgery seems to offer more predictable and curative results [16,18]. However, surgical treatment for early-stage BRONJ remains controversial.

The PP 2017 recommends osteotomy as a treatment option for patients with intractable stage 2 BRONJ, which was previously indicated only for patients with stage 3 BRONJ, as well as the removal of sequestra and curettage of necrotic bone [1].

As BRONJ is a serious side effect of BPs treatment, it may be necessary to change BPs treatment to alternative medications in affected patients, if available [1]. Indeed, we previously reported that a case of BRONJ caused by low-dose BP treatment for osteoporosis was effectively treated using the alternative medication teriparatide [19].

The nonsurgical management of BRONJ is aimed at improving the stage of the disease and avoiding its progression. Nonsurgical options include the use of antimicrobial mouth rinses, local disinfection/cleaning of exposed bone and fistulae, pain control,

and the administration of antibiotics and nutritional support when required. In the presence of exposed bone, superficial debridement may be useful for reducing sharp edges and relieving soft tissue irritation. Even for cases in which surgery is indicated, nonsurgical management before and after surgery (i.e., during the perioperative period) is critical. As surgery is not indicated for all patients with BRONJ, further research is required to identify the most appropriate methods of nonsurgical management.

Healing following BRONJ treatment is defined based on clinical evidence of stable oral mucosal coverage—a criterion adopted by the vast majority of surgical studies [18,20]. However, oral mucosal coverage does not necessarily reflect the absence of underlying necrotic bone. Despite several studies that have suggested that a clinical follow-up period of 6 months is sufficient for confirming a cure, there is increasing evidence that some BRONJ may recur 1 year or more after the completion of surgery [18,20,21].

In most cases, it is generally recommended to completely close the surgical wound following the removal of a lesion, and a wound is often assessed as having healed if there is no dehiscence. However, as previously mentioned, some recurrence are observed more than 1 year following BRONJ treatment. Such findings may be due to the presence of remaining necrotic bone underneath the mucosa, despite the appearance of having achieved healing at the soft tissue level after complete closure.

2.4. Prevention of BRONJ

Management of oral hygiene, patient education, and providing proper dental treatment are critical for preventing BRONJ [1]. However, whether a preventative drug holiday is useful during tooth extraction for patients receiving BPs remains controversial. Although little evidence suggests that temporary cessation of BPs treatment is effective for preventing BRONJ (as reported in the AAOMS 2014), the PP 2017 proposes that discontinuation of BPs treatment for approximately 2 months should be considered in patients at high risk for BRONJ who have received BPs for more than 4 years, provided they also exhibit a low risk for fracture. This option should be considered prior to invasive dental treatment, in consultation with the patient's physician [1].

However, several studies have not supported the use of a drug holiday, and there is little clinical evidence that short-term discontinuation of BPs helps to prevent the occurrence of BRONJ following invasive dental treatments. Based on the physicochemical properties of BPs, which are deposited and persist in the bone for a long period of time [22], it is unlikely that a short-term BPs drug holiday can prevent BRONJ. Moreover, cessation of treatment may exacerbate osteoporosis by decreasing bone mineral density and increasing the risk of fractures [23,24]. Given the extremely low incidence of BRONJ among patients with osteoporosis, the benefits of BPs for fracture prevention outweigh the risks of BRONJ [25].

Several recent studies have reported that infection is a key event in the development of BRONJ, and that extensive infection control prior to invasive dental treatment reduces the risk of BRONJ [26]. Researchers have suggested that a reduction in the intraoral bacterial load plays an important role in BRONJ prevention, as it may minimize the risks of secondary infection in exposed bone and disease progression. Important aspects of oral management include not only assessments of oral hygiene, but also assessments for the presence of periapical lesions, periodontal disease, or lesions of the jawbone. X-ray examination is indispensable for evaluating the alveolar bone and jaw, as these are covered with soft tissue and cannot be viewed directly. If necessary, proper dental treatment should be provided based on assessment of oral findings, and patients with BRONJ should be advised regarding the importance of preventive oral care (i.e., removal of supra- and sub-gingival dental plaque, scaling, root planning) and maintaining good oral hygiene. Optimal oral hygiene requires appropriate motivation, adequate tools, and professional instruction.

3. Insight into the definition of BRONJ

As noted in the PP 2017, ARONJ (which includes BRONJ) is definitively diagnosed when the following three conditions are met [1]:

i. History of treatment with BPs or denosumab.
ii. No history of radiation therapy to the jaw. Bone lesions associated with ARONJ must be differentiated from cancer metastasis to the jawbone via histological examination.
iii. Exposure of alveolar bone in the oral cavity, jaw, and/or face is continuously observed for longer than 8 weeks after first detection by a medical or dental expert, or the bone is palpable in the intraoral or extraoral fistula for longer than 8 weeks. These criteria do not apply to stage 0 ARONJ.

In 2014, the AAOMS proposed additional diagnostic criteria for ONJ [8]. In addition to BPs and denosumab, criterion (i) now applies to bevacizumab and sunitinib (AAOMS 2014).

3.1. Ruling out malignancies and osteoradionecrosis of the jawbone

The PP 2017 specifies that bone lesions associated with ARONJ must be differentiated from cancer metastasis to the jawbone via histological examination (criterion ii). Thus, the possibility of not only metastatic but also primary cancers should be considered. Patients undergoing BPs treatment against bone metastasis of breast or prostate cancer are monitored for metastasis to the jawbone. However, patients taking BPs for osteoporosis are also at risk for misdiagnosis of BRONJ due to failed healing following tooth extraction, the presence of exposed bone under a denture base, or spontaneous tooth loss. The potential for misdiagnosis of gingival cancer or osseocentric carcinoma of the jawbone as BRONJ should be considered in long-term local irrigation cases.

Outcomes from radiation therapy for head and neck cancer have improved, and the number of long-term survivors continues to increase. However, the number of patients who develop late-onset ONJ and disturbances of salivary secretion has also increased. If a patient whose jawbone is affected by radiation therapy is also given BPs and develops ONJ, it is not easy to determine whether the disease is due to radiation or BPs treatment. Nonetheless, the current definition emphasizes the effects of radiation (criterion ii). Comprehensive judgments should be made by evaluating the accumulated BPs dosage and total radiation dosage at the site of osteonecrosis.

3.2. Stage 0 diagnosis

Several reports have discussed stage 0 BRONJ. The AAOMS 2014 proposed that patients with ONJ-like clinical manifestations but no alveolar bone exposure should be diagnosed with stage 0 ONJ, and that stage 0 cases should be diagnosed and treated as pre-ONJ [8]. Although this stage is reported to account for 25–30% of ONJ cases, half of stage 0 cases may never progress to apparent bone exposure [27]. Accordingly, the International Task Force on ONJ does not include stage 0 in the diagnostic criteria for ONJ, as this may lead to overdiagnosis [2].

Although the AAOMS and the International Task Force on ONJ take different positions regarding ONJ diagnosis, Japan's PP 2017 includes ONJ stage 0, which is consistent with the AAOMS proposal from a therapeutic point of view [1]. When stage 0 is included, the presence of palpable bone at the site of the fistula may increase the risk of overdiagnosis, as the fistula may be due to apical or marginal

Table 1
Treatments based on bisphosphonate-related osteonecrosis of the jaw (BRONJ) staging (quoted with modification from document 1).

	Clinical symptoms and Imaging findings	Treatment
Stage 0	Clinical symptoms: no bone exposure/necrosis, deep periodontal pocket, loose tooth, oral mucosal ulcer, swelling, abscess formation, trismus, hypoesthesia/numbness of the lower lip (Vincent's symptom), non-odontogenic pain Imaging findings: sclerotic alveolar bone, thickening and sclerosis of lamina dura, remaining tooth extraction socket	Use of antimicrobial mouthwash, rinsing and cleaning of fistula and periodontal pocket, and topical application or injection of local antimicrobial agents
Stage 1	Clinical symptoms: asymptomatic bone exposure/necrosis without sign of infection, or fistula in which the bone is palpable with a probe Imaging findings: sclerotic alveolar bone, thickening and sclerosis of lamina dura, remaining tooth extraction socket	
Stage 2	Clinical symptoms: bone exposure/necrosis associated with pain, infection, fistula in which bone is palpable with a probe or at least one of the follwoing symptoms including bone exposure/necrosis over the alveolar bone (e.g. reaching the mandibular inferior edge or mandibular ramus, or reaching the maxillary sinus or mandibular ramus or the cheek bone), which result in pathologic fracture, extraoral fistula, nasal/maxillary sinus fistula formation, or advanced osteolydis extending to the mandibular inferior edge or maxillary sinus.	Combination of antimicrobial mouthwash and agents; intractable case: combination of multiple antimicrobial agents, long-term antimicrobial administration, continuous administration of intravenous antimicrobial agents, removal of sequestra, curettage of necrotic bones, and osteotomy
Stage 3	Clinical symptoms: bone exposure/necrosis associated with pain, infection, or at least one of the following symptoms, or fistula in which bone is palpable with a probe. Bone exposure/necrosis over the alveolar bone (e.g. reaching the mandibular inferior edge or mandibular ramus, or reaching the maxillary sinus or mandibular ramus or the cheek bone). As a result, pathologic fracture or extraoral fistula, nasal/maxillary sinus fistula formation, or advanced osteolysis extending to the mandibular inferior edge or maxil- lary sinus Imaging findings: osteosclerosis/osteolysis of the surrounding bone (cheek bone, palatine bone), pathologic mandibular fracture, and osteolysis extending to the maxillary sinus floor	Removal of sequestra, curettage of necrotic bones, osteotomy, extraction of tooth in exposed bone/necrotic bone as source of infec- tion, maintenance of nutrition with supplements and infusions, and marginal or segmental resection of expanding necrotic bones

periodontitis rather than BRONJ. Indeed, it is difficult to clinically differentiate between a fistula caused by periapical lesion or periodontal disease and a fistula caused by BRONJ. Excessive treatment due to overdiagnosis should be strongly discouraged. However, treatment should not be delayed by a failure to diagnose BRONJ in the absence of exposed or palpable bone.

When hypoesthesia/numbness of the lower lip (Vincent's symptom) is observed in the absence of exposed bone, the patient taking BPs are diagnosed as stage 0 BRONJ. In the PP2017, stage 0 BRONJ without bacterial infection – being milder than stage 1 BRONJ – are treated as follows: treatment using antimicrobial mouthwash, rinsing and cleaning of the fistula and periodontal pocket, and topical application or injection of local antimicrobial agents. One current problem in the treatment of stage 0 BRONJ with Vincent's symptom is that systemic administration of antimicrobials is not recommended in such cases. If Vincent's symptom are regarded as a symptom of mandibular osteomyelitis, treatment in stage 2 strategies should be recommended: combined treatment with multiple antimicrobial agents, long-term antimicrobial treatment, or continuous administration of intravenous antimicrobial agents (Table 1).

4. Development and typing of BRONJ

Although the pathophysiology of BRONJ remains unclear, several theories have been proposed [28,29]. Previous studies have indicated that BRONJ may be due to decreases in bone turnover, the presence of infection (e.g., *Actinomyces* infection), inhibition of angiogenesis, and dysregulation or dysfunction of innate and acquired immunity. Putative causes of BRONJ include a complex association of multiple factors, rather than a single factor such as the invasiveness of tooth extraction. With the exception of necrosis of the external auditory canal [30] – which is extremely rare – occurrence exclusively in the jawbone may be attributed to the uniqueness of the oral cavity and jawbone.

Drug package inserts in Japan list "osteonecrosis of the jaw" and "osteomyelitis of the jaw" as serious side effects of BPs. Although the name for BRONJ is derived from osteonecrosis, cases typically involve refractory suppurative osteomyelitis with bacterial infection.

4.1. Uniqueness of the oral cavity and jawbone

Although it remains unclear why BRONJ specifically affects the jawbone, several unique anatomical and microbiological characteristics of the oral cavity and jawbone may be responsible. In the human skeltone, the jawbones is one of the least-protected bones from infection. Indeed, the alveolar bones in both the mandible and maxilla are separated from the pathogens of the oral mucosal lesion by a thin layer of periosteum and an epithelium with an attenuated layer of connective tissue only, whereas deep soft tissues and skin protect other bones.

Moreover, the oral structures are subjected to a wide variety of physiologic (e.g., mastication), iatrogenic (e.g., invasive dental procedures), and inflammatory (e.g., periodontal disease, periapical lesion) stressors. This combination of constant stress not only predisposes the thin mucosa to trauma, leading to bone exposure, but likely demands an increase in metabolic compensation for bone remodeling.

Furthermore, the oral cavity and teeth are colonized by a complex microbial flora that includes pathogenic organisms. The relationship of the teeth to the jawbone allows for the entry of microbes and other inflammatory products to the underlying bone—a scenario that is not observed in other regions of the body.

The role of specific microbes in the development of BRONJ has yet to be fully elucidated. Notably, several authors have documented the presence of *Actinomyces* in patients with BRONJ, leading Naik and Russo [31] to suggest a critical role of this organism in the development of ONJ. It remains unclear, however, whether actinomycotic colonization occurs as a primary event or as a secondary phenomenon due to its prevalence in the oral cavity.

4.2. Osteonecrosis type

The term "osteonecrosis" is associated with aseptic necrosis. Stage 1 BRONJ does not involve bacterial infection (Table 1). There-

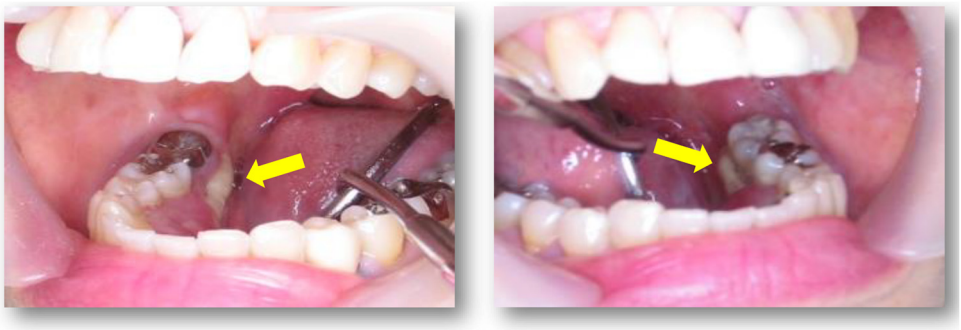

Figure 2. Bilateral BRONJ is difficult to distinguish from OUBS.
BRONJ: bisphosphonate-related osteonecrosis of the jaw.
OUBS: oral ulceration and benign sequestration/oral ulceration with bone sequestration.

fore, stage 1 BRONJ can be defined as "osteneonecrosis type" of BRONJ. On the other hand, typical development of BRONJ is thought to a worsening of suppurative osteomyelitis of the jaw (i.e., bacterial infection). Thus, this "osteomyelitis type" of BRONJ bypass stage 1.

Stage 1 BRONJ often involves the exposure of bone at an exostosis of the torus mandibularis, torus palatinus, or mylohyoid line (Fig. 2). Although BRONJ may occur in these areas due to the relatively thin mucosa, the onset of BRONJ may be associated with the strength of the occlusal force [32], which may produce an exostosis. That is, strong occlusal forces associated with mastication and bruxism result in a greater level of active bone remodeling at the exostosis, in turn resulting in greater accumulation and deposition of BPs to the jawbone.

The term osteonecrosis is often used interchangeably with ischemic necrosis, avascular necrosis, or aseptic necrosis. Although the pathophysiology of BRONJ remains unclear, it is consistent with the finding that aseptic osteonecrosis due to ischemic changes (e.g., decreased bone vascularity and/or inhibition of angiogenesis due to BPs) often occurs at sites with considerable accumulation/deposition of BPs to the jawbone.

While preventive countermeasures are available for osteomyelitis of the jaw derived from odontogenic infection, preventive dental measures cannot prevent the onset of the osteonecrotic type of BRONJ itself, which is a drug induced, true pharmacological side effect of BPs treatment. Approximately 20% of BRONJ cases in Japan are classified as stage 2, although this rate depends on the definition of BRONJ and whether classification schemes include stage 0 BRONJ. Preventing secondary infection and lesion progression is a critical strategy for preventing both osteonecrotic and osteomyelitic BRONJ.

4.3. *Osteomyelitic BRONJ*

BRONJ can be classified into an osteomyelitic type, which involves infection, and an osteonecrotic type, which does not involve infection originally. Osteomyelitic BRONJ is thought to occur following the administration of BPs in patients with odontogenic bacterial infection, which results in a transition to osteomyelitis of the jaw or worsens the symptoms of an existing osteomyelitic infection (Fig. 3). Although this type clearly differs from osteonecrosis type of BRONJ, patients with stage 1 osteonecrotic BRONJ may develop infection, thereby progressing to stage 2 or 3. Thus, the exact ratio between the two types of BRONJ remains unknown; however, the rate of osteomyelitic BRONJ due to odontogenic infection is empirically higher than that of the osteonecrosis type in Japan. Bone scintigraphy should be used to monitor patients with persistent chronic inflammation due to local infection, as the accumulation of BPs at the site of inflammation may increase the risk of BRONJ.

During the early stages of osteomyelitis, it is important to identify the causative microbes so that appropriate antibiotics can be selected. Nonetheless, refractory osteomyelitis of the jaw is a biofilm infection, and most cases of BRONJ are associated with irreversible necrotic changes to the bone, meaning that some form of surgical intervention is necessary, barring spontaneous discharge of the sequestra. Thus, the importance of antimicrobial therapy can be regarded as relatively low. However, it is possible to significantly reduce the risk of osteomyelitic BRONJ by preventing periodontal disease, periapical lesion, pericoronitis, dental peri-implantitis, and other forms of odontogenic infection. The rate of osteomyelitic BRONJ could also be reduced by performing tooth extraction or removing infected dental implants when indicated.

5. Indications for invasive dental treatment in patients receiving BPs

Tooth extraction is the most reliable countermeasure of eliminating the source of infection in patients with or at risk for osteomyelitis. Section 2.4 discusses the implementation of a preventive drug holiday from BPs for 2-3 months prior to tooth extraction. However, the risk for the progression of odontogenic infection must also be considered during the interval prior to tooth extraction.

5.1. *Development of BRONJ due to tooth extraction*

The PP 2017 mentions six risk factors for ONJ: 1) invasive dental treatment to the jawbone via tooth extraction, implant placement, periapical surgery, periodontal surgery, etc. (i.e., locality); 2) treatment with antiresorptive agents; 3) systemic nature; 4) congenital nature; 5) lifestyle; and 6) use of concomitant medications [1]. Considering that tooth extraction in particular is believed to be the trigger for onset in 67% of BRONJ cases [33], and that tooth extraction is reportedly associated with a higher incidence of BRONJ [34], this risk factor is thought to be more important than the type or cumulative dose of antiresorptive agents. Our previous studies have reproduced the pathological characteristics of BRONJ in diabetic rats that had received the BPs zoledronic acid prior to tooth extraction [35]. It is thought that invasive bone surgery should be avoided to the greatest extent possible in patients undergoing treatment with BPs. Such recommendations are outlined in the PP 2017, as well as the drug package inserts fort BPs.

However, BRONJ often occurs when no tooth extraction has been performed, and drug package inserts note that many reported cases of BRONJ occur following both "invasive dental treatment involving the jawbone" and "local infection". Most tooth extractions are per-

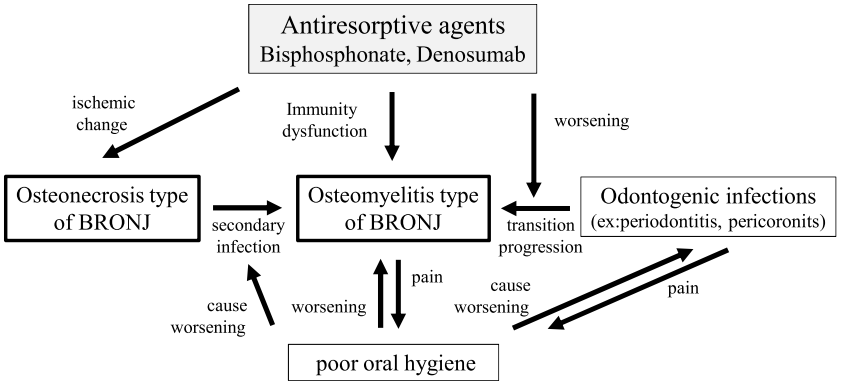

Figure 3. Relationship between osteonecrosis type and osteomyelitis type of BRONJ.

formed due to existing periodontal disease and/or periapical lesion. The AAOMS 2014 also states that inflammatory dental diseases such as periodontal disease and periapical lesion are well-known risk factors for MRONJ, and that inflammatory dental disease is observed at onset in 50% of patients with cancer who develop MRONJ. Thus, inflammatory dental disease should be considered a potential risk factor for the onset of MRONJ after tooth extraction [8].

Based on these findings, we speculate that local infection associated with tooth extraction may be a greater risk factor for BRONJ than surgical invasiveness. It is possible that diagnoses of BRONJ after tooth extraction are in fact cases of stage 0 BRONJ lesions. Such cases represent a form of "latent BRONJ", which is difficult to diagnose prior to tooth extraction. In some cases, refraining from tooth extraction may prolong local infection, leading to the development of BRONJ. We therefore propose that the relative importance of tooth extraction as a risk factor for BRONJ has been overstated.

As the incidence of BRONJ is low, there is no need to be overly cautious of tooth extraction in patients taking BPs, especially at low doses. If it is difficult to control chronic inflammation without tooth extraction, the tooth should be extracted with proper monitoring for postoperative infection, appropriate oral management prior to extraction including preoperative prophylactic administration of antimicrobials. Not performing tooth extraction may increase the patient's risk for the onset and progression of osteomyelitic BRONJ.

Several reports have indicated that incomplete wound closure is associated with an increased risk of BRONJ. However, Mozzati et al. prospectively compared two surgical protocols for tooth extraction with different degrees of invasiveness among patients treated with oral BPs [36]. Patients who required removal of compromised teeth were randomly assigned to one of two groups: A total of 334 were treated via delicate surgery and closure by primary intention (Protocol A), while the remaining 366 were treated via nontraumatic avulsion and closure by secondary intention (Protocol B). All patients were administered with antibiotic coverage. There was no evidence of postoperative BRONJ in either group at follow-up for at least 12 months (1480 extractions), suggesting that both protocols can provide predictable treatment outcomes in patients treated with oral BPs. Therefore, because atraumatic surgery is more comfortable for patients, Mozzati et al. recommended the adoption of Protocol B, which limits trauma to both the soft and hard tissues.

The authors are currently conducting a prospective study of tooth extraction without a drug holiday for patients taking oral BPs, but have yet to observe a case of BRONJ following incomplete closure of the extraction socket wound [37]. Complete would closure may therefore be unnecessary. As stated in Section 2.3, complete wound closure may mask the presence of necrotic bone underneath the mucosa.

5.2. Onset of BRONJ due to dental implantation

The PP 2017 states the following: "Recent reports suggest that dental implantation procedures performed in patients with cancer or osteoporosis prior to treatment with BPs are not likely associated with subsequent occurrence of BRONJ, if oral health is appropriately managed [38,39]. However, dental implantation performed during or after BP treatment is a potential risk factor for BRONJ" [1]. These findings indicate that improper overdentures with implants, or peri-implantitis, should also be regarded as a potential risk factor, even when dental implantation has been performed prior to BPs administration.

Kwon et al. reported that dental implant-related BRONJ can be divided into two types [40]. In the implantation surgery-triggered type, onset occurs less than 6 months after implantation surgery and is believed to be associated with surgical invasiveness. In the non-surgery-triggered type, BRONJ develops more than 6 months after surgery or following the initiation of postoperative treatment with antiresorptive agents.

The PP 2017 states the following: "Implants are not advised for cancer patients who are receiving antiresorptive treatment, and alternative dental measures are recommended. On the other hand, in patients with osteoporosis, dental implantation may be performed in cases in which physicians and dentists agree that dental implants are essential for improving the systemic and oral health of patients". BRONJ occurs infrequently following dental implant surgery. For patients taking low doses of BPs, dental implant surgery is not necessarily contraindicated if there are no other risk factors such as combined use of corticosteroids or concomitant diabetes. As there is not only a risk of developing BRONJ at the time of implantation surgery, but also a risk of BRONJ due to late-onset peri-implantitis, a full explanation of these risks must be provided when obtaining consent from patients.

As the average lifespan continues to increase, the incidence of BRONJ secondary to peri-implantitis is expected to increase as well. Predictions of prognosis based on oral assessments are important when beginning BP treatment in patients with dental implants. If necessary, options such as removal of the implants provoking peri-implantitis, modification of the superstructure, and other treatment strategies should be explored.

6. Conclusions

1) The presence of exposed bone in patients undergoing treatment with BPs does not necessarily reflect BRONJ, and diagnoses of

OUBS and malignancy must be excluded. Although overdiagnosis based on the presence of palpable bone through the fistula is a matter of concern, some cases of ONJ do not involve exposed bone, so diagnosis should not be delayed.

2) Osteonecrotis type of BRONJ, which is regarded as a true side effect of BP treatment, is difficult to avoid using preventive dental measures alone. However, as with osteomyelitis type of BRONJ, preventive dental measures are indispensable for reducing the risk of secondary infection and disease progression.
3) The importance of tooth extraction as a risk factor for BRONJ among patients taking BPs has been overstated, particularly when they are administered at low doses. If it would be difficult to control chronic inflammation without tooth extraction, tooth extraction should be performed while taking measures to prevent infection, such as the use of preoperative, prophylactic antimicrobials. Delaying tooth extraction may increase the risk for the onset and progression of osteomyelitic BRONJ.
4) In patients taking low doses of BPs, dental implant surgery is not contraindicated if there are no other risk factors, such as combined use of corticosteroids or concomitant diabetes. However, the risk of BRONJ due to peri-implantitis must be explained when obtaining patient consent.

Conflict of interest

Hiromitsu Kishimoto: lecture fee (Asahi Kasei Pharma, Daiichi-Sankyo, Chugai Pharmaceutical, Teijin Pharma). Kazuma Noguchi: none. Kazuki Takaoka: none.

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References

[1] Yoneda T, Hagino H, Sugimoto T, Ohta H, Takahashi S, Soen S, et al. Antiresorptive agent-related osteonecrosis of the jaw: position paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. J Bone Miner Metab 2017;35(1):6–19.
[2] Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, et al. International task force on osteonecrosis of the jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Mineral Res 2015;30(1):3–23.
[3] Qi WX, Tang LN, He AN, Yao Y, Shen Z. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. Int J Clin Oncol 2014;19:403–10.
[4] Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003;61:1115–7.
[5] Urade M, Tanaka N, Furusawa K, Shimada J, Shibata T, Kirita T, et al. Nationwide survey for bisphosphonate-related osteonecrosis of the jaws in Japan. J Oral Maxillofac Surg 2011;69:e364–71.
[6] Shibahara T, Morikawa T, Yago K, Kishimoto H, Imai Y, Kurita K. National survey on bisphosphonate-related osteonecrosis of the jaws in Japan. J Oral Maxillofac Surg 2018;76:2105–12, http://dx.doi.org/10.1016/j.joms.2018.04.009 (Published online: April 13, 2018).
[7] Yoneda T, Hagino H, Sugimoto T, Ohta H, Takahashi S, Soen S, et al. Bisphosphonate-related osteonecrosis of the jaw: position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons. J Bone Miner Metab 2010;28:365–83.
[8] Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw——2014 update. J Oral Maxillofac Surg 2014;72(10):1938–56.
[9] Chiu CT, Chiang WF, Chuang CY, Chang SW. Resolution of oral bisphosphonate and steroid-related osteonecrosis of the jaw—a serial case analysis. J Oral Maxillofac Surg 2010;68(5):1055–63.
[10] Powell C, Chang C, Gershwin ME. Current concepts on the pathogenesis and natural history of steroid-induced osteonecrosis. Clin Rev Allergy Immunol 2011;41(1):102–13.
[11] Horie N, Kawano R, Kaneko T, Shimoyama T. Methotrexate-related lymphoproliferative disorder arising in the gingiva of a patient with rheumatoid arthritis. Aust Dent J 2015;60(3):408–11.
[12] Henien M, Carey B, Hullah E, Sproat C, Patel V. Methotrexate-associated osteonecrosis of the jaw: a report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124(6):e283–7.
[13] Seyer BA, Grist W, Muller S. Aggressive destructive midfacial lesion from cocaine abuse. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94(4):465–70.
[14] Rustemeyer J, Melenberg A, Junker K, Sari-Rieger A. Osteonecrosis of the maxilla related to long-standing methamphetamine abuse: a possible new aspect in the etiology of osteonecrosis of the jaw. Oral Maxillofac Surg 2014;18(2):237–41.
[15] Farah CS, Savage NW. Oral ulceration with bone sequestration. Aust Dent J 2003;48(1):61–4.
[16] Kühl S, Walter C, Acham S, Pfeffer R, Lambrecht JT. Bisphosphonate-related osteonecrosis of the jaws—a review. Oral Oncol 2012;48(10):938–47.
[17] Van den Wyngaert T, Claeys T, Huizing MT, Vermorken JB, Fossion E. Initial experience with conservative treatment in cancer patients with osteonecrosis of the jaw (ONJ) and predictors of outcome. Ann Oncol 2009;20(2):331–6.
[18] Carlson ER, Basile JD. The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2009;67(5 Suppl):85–95.
[19] Zushi Y, Takaoka K, Tamaoka J, Ueta M, Noguchi K, Kishimoto H. Treatment with teriparatide for advanced bisphosphonate-related osteonecrosis of the jaw around dental implants: a case report. Int J Implant Dent 2017;3(1):11.
[20] Wilde F, Heufelder M, Winter K, Hendricks J, Frerich B, Schramm A, et al. The role of surgical therapy in the management of intravenous bisphosphonates-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111(2):153–63.
[21] Bedogni A, Saia G, Bettini G, Tronchet A, Totola A, Bedogni G, et al. Long-term outcomes of surgical resection of the jaws in cancer patients with bisphosphonate-related osteonecrosis. Oral Oncol 2011;47(5):420–4.
[22] Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011;48(4):677–92.
[23] Taguchi A, Shiraki M, Sugimoto T, Ohta H, Soen S. Japan Osteoporosis Society. Lack of cooperation between physicians and dentists during osteoporosis treatment may increase fractures and osteonecrosis of the jaw. Curr Med Res Opin 2016;32(7):1261–8.
[24] Curtis JR, Westfall AO, Cheng H, Delzell E, Saag KG. Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday. Osteoporos Int 2008;19(11):1613–20.
[25] Black DM, Rosen CJ. Clinical Practice. Postmenopausal Osteoporosis. N Engl J Med 2016;374(3):254–62.
[26] Otto S, Tröltzsch M, Jambrovic V, Panya S, Probst F, Ristow O, et al. Tooth extraction in patients receiving oral or intravenous bisphosphonate administration: a trigger for BRONJ development? J Craniomaxillofac Surg 2015;43(6):847–54.
[27] Fedele S, Porter SR, D'Aiuto F, Aljohani S, Vescovi P, Manfredi M, et al. Nonexposed variant of bisphosphonate-associated osteonecrosis of the jaw: a case series. Am J Med 2010;123(11):1060–4.
[28] Landesberg R, Woo V, Cremers S, Cozin M, Marolt D, Vunjak-Novakovic G, et al. Potential pathophysiological mechanisms in osteonecrosis of the jaw. Ann N Y Acad Sci 2011;1218:62–79.
[29] Sarin J, DeRossi SS, Akintoye SO. Updates on bisphosphonates and potential pathobiology of bisphosphonate-induced jaw osteonecrosis. Oral Dis 2008;14(3):277–85.
[30] Thorsteinsson AL, Vestergaard P, Eiken P. External auditory canal and middle ear cholesteatoma and osteonecrosis in bisphosphonate-treated osteoporosis patients: a Danish national register-based cohort study and literature review. Osteoporos Int 2014;25:1937–44.
[31] Naik NH, Russo TA. Bisphosphonate-related osteonecrosis of the jaw: the role of *Actinomyces*. Clin Infect Dis 2009;49:1729–32.
[32] Yoshinaka M, Ikebe K, Furuya-Yoshinaka M, Maeda Y. Prevalence of torus mandibularis among a group of elderly Japanese and its relationship with occlusal force. Gerodontology 2014;31(2):117–22.
[33] Filleul O, Crompot E, Saussez S. Bisphosphonate-induced osteonecrosis of the jaw: a review of 2,400 patient cases. J Cancer Res Clin Oncol 2010;136:1117–24.
[34] Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis CG, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J Clin Oncol 2009;27:5356–62.
[35] Takaoka K, Yamamura M, Nishioka T, Abe T, Tamaoka J, Segawa E, et al. Establishment of an animal model of bisphosphonate-related osteonecrosis of the jaws in spontaneously diabetic Torii rats. PLoS One 2015;10:e0144355.
[36] Mozzati M, Arata V, Gallesio G. Tooth extraction in osteoporotic patients taking oral bisphosphonates. Osteoporos Int 2013;24(5):1707–12.
[37] Shudo A, Kishimoto H, Takaoka K, Noguchi K. Long-term oral bisphosphonates delay healing after tooth extraction: a single institutional prospective

study. Osteoporos Int 2018, http://dx.doi.org/10.1007/s00198-018-4621-7 (Accepted).
[38] Holzinger D, Seemann R, Matoni N, Ewers R, Millesi W, Wutzl A. Effect of dental implants on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2014;72(1937):e1–8.
[39] Matsuo A, Hamada H, Takahashi H, Okamoto A, Kaise H, Chikazu D. Evaluation of dental implants as a risk factor for the development of bisphosphonate-related osteonecrosis of the jaw in breast cancer patients. Odontology 2016;104:363–71.
[40] Kwon TG, Lee CO, Park JW, Choi SY, Rijal G, Shin HI. Osteonecrosis associated with dental implants in patients undergoing bisphosphonate treatment. Clin Oral Implants Res 2014;25:632–40.