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Review

Medication-Related Osteonecrosis of the Jaws: Review

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Introduction

Medication-related osteonecrosis of the jaw (MRONJ) results from infection and side effect by antiresorptive agents and angiogenesis inhibitors that it causes healing failure of the upper and lower jaw and soft tissue [1,2]. The approaches to dental issues and treatment of MRONJ showed reduced incidence and severity, but MRONJ may still adversely affects quality of life (QOL) and produces substantial morbidity [3]. The current national survey revealed a rapid rise in the number of cases of MRONJ in recent years in Japan [4]. This report presents; 1) pathophysiology of the disease, 2) therapy of MRONJ, and 3) management of MRONJ, mainly.

Cause Medicine

The cause medicine of MRONJ are antiresorptive agents and angiogenesis inhibitor [1]. Antiresorptive agents are included bisphosphonates (BPs) and denosumab (Dmab) [5]. BPs, which possess a high chemical affinity for bone and specifically inhibit osteoclastic bone resorption, have been widely and safely used for the treatment of oncology, such as bone metastasis [5-13] and osteoporosis [5, 14-19] in which an excessive increase in osteoclastic bone resorption occurs. Dmab, a human IgG2 monoclonal antibody against receptor activator of nuclear factor-kappa B ligand (RANKL), is a therapeutic agent for oncology, such as bone metastasis [5, 20, 21] and osteoporosis [5, 18, 19, 22, 23], with a half-life of approximately 1 month. Unlike BPs, which promote apoptosis in osteoclasts, Dmab inhibits osteoclastic bone resorption without causing apoptosis. Angiogenesis inhibitors are molecularly targeted drugs, such as bevacizumab (Bmab), sunitinib and sorafenib, sirolimus. Also, the American Association of Oral and Maxillofacial Surgeons (AAOMS) encourages the need for caution with similarly acting drugs [1].

ONJ causes drugs by cause medicine, patients treated with BPs also developed ONJ (BPs-related osteonecrosis of the jaw: BRONJ), Dmab developed ONJ (Dmab-related osteonecrosis of the jaw: DRONJ), antiresorptive agents also developed ONJ (antiresorptive agents related osteonecrosis of the jaw: ARONJ).

Diagnosis of ARONJ

AAOMS and the Allied Committee, Japanese Allied Committee on Osteonecrosis of the Jaw released Position Paper in 2014 and 2017 [1, 2]. Accordingly, MRONJ is definitively diagnosed when the following three conditions are met:

1. Patients have a history of treatment with antiresorptive agents or antiangiogenic inhibitors;
2. Patients have no history of radiation therapy to the jaw. Bone lesions of MRONJ must be differentiated from cancer metastasis to the jawbone by histological examination; and
3. Exposed bone in the oral cavity or bone that can be probed through intra- and/or extra-oral fistulae in the maxillofacial region that has persisted for more than eight weeks after first detection by a medical or dental expert. These criteria do not apply to Stage 0 of MRONJ.

Pathophysiology of the Disease

Although the first MRONJ case was reported over a decade ago, the pathophysiology of the disease has not been fully elucidated [24]. A source of great debate among clinicians and researchers are the potential mechanisms underlying MRONJ pathophysiology.

The cause of MRONJ is thought that osteoclastic bone resorption and remodeling inhibition, inflammation or infection, angiogenesis inhibition, suppression of immunity and soft tissue BP toxicity.

Osteoclastic bone resorption and remodeling inhibition

Antiresorptive agents inhibit osteoclast differentiation and function, and increase apoptosis, all leading to decreased bone resorption and remodeling. The differentiation and function of osteoclast play vital role in bone

healing and remodeling in all skeletal sites. However, ONJ develop primarily within the bone of the maxilla and mandible mainly. The role of bone remodeling inhibition is further corroborated by a similar incidence of ONJ observed with BP and Dmab [20, 21, 25].

Inflammation/Infection

Both systemic and local oral risk factors have been implicated in MRONJ pathogenesis, where several human studies have implicated dental disease or bacterial infection [26-28]. Although tooth extraction was risk factor of MRONJ, these teeth commonly had existing periodontal or periapical disease [4, 26, 29, 30]. Inflammation/infection is an important component of MRONJ. Especially, *Actinomyces* colonies are frequently present in contact with necrotic bones in MRONJ lesions, raising the possibility that *Actinomyces* bacteria play a role in the pathogenesis of MRONJ [31]. These bacteria perform biofilm on exposed bone of the MRONJ. Surgical therapy works effectively to remove this biofilm [32].

Angiogenesis inhibition

Angiogenesis is a process to form new blood vessels. Angiogenesis influences tumor growth and invasion, metastasis. Osteonecrosis is classically considered an interruption in vascular supply or avascular necrosis [33-36]. It was reported a reduction of angiogenesis in oncology patients treated with zoledronic acid [37]. Moreover, it was growing on ONJ that in patients receiving novel antiangiogenic inhibitors such as Bmab, sunitinib and sorafenib, sirolimus. However, angiogenesis inhibition has not been reported with Dmab.

Suppression of immunity

In animal model, ONJ was not confirmed to occur with only BP [38]. For development of ONJ, there are required, such as glucocorticoid steroids and chemotherapeutic drugs, suggesting involvement of immunosuppression.

Soft tissue toxicity

Although BPs primarily target the osteoclast and bind to hydroxyapatite in bone, soft tissue toxicity has been reported [39-41]. Most of the BP is excreted in the kidney after several hours after administration. Therefore, the blood concentration of BP decreases promptly [42]. In contrast to BP's, no soft tissue toxicity has been reported with Dmab.

Incidence of MRONJ

In general, it reported that the incidence of onset of MRONJ was low. The reported incidence of MRONJ varies by study, and there are no reliable epidemiological data derived from evidence-based medicine (EBM). This review follows the data cited by the International Task Force on ONJ [43, 44].

Osteoporosis

Osteoporosis

The frequency of ONJ in osteoporosis patients received oral BPs at 0.001% to 0.21% [43-49]. The frequency of ONJ in osteoporosis patients received Dmab at 0.02% [43, 44, 50].

Oncology

The frequency of ONJ in oncology patients receiving oncology doses of BP or Dmab is estimated at 0.7% to 15% [43, 44, 51-60]. The risk of ONJ among oncology patients exposed to zolendronate ranges between 50-100 times higher than oncology patients treated with placebo. The risk for ONJ among oncology patient exposed to Dmab is comparable to the risk of ONJ in patients exposed to zoledronate [48].

However, the incidence of MRONJ in patients with oncology versus osteoporosis could not be compared. This should be evaluated in future studies.

Therapy of MRONJ

MRONJ is currently classified into four stages depending on its severity, discharge of pus, and pain [1, 2]. Stage of MRONJ was shown follows (Table 1);

Stage 0: Clinical symptoms were no bone exposure/necrosis, deep periodontal pocket, loose tooth, Vincent's symptom, non-odontogenic pain. Imaging findings were sclerotic alveolar bone, thickening and sclerosis of lamina dura, remaining tooth extraction socket.

Stage 1: Clinical symptoms were asymptomatic bone exposure/necrosis without sign of infection and pain, or fistula in which the bone is palpable with a probe. And imaging findings were sclerotic alveolar bone, thickening and sclerosis of lamina dura, remaining tooth extraction socket.

Stage 2: Clinical symptoms were bone exposure/necrosis associated with pain, infection, fistula in which bone is palpable with a probe.

and Stage 3: Clinical symptoms were 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, such as reaching the mandibular ramus or reaching the maxillary sinus 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 maxillary sinus. And imaging findings: osteosclerosis/osteolysis of the surrounding bone (cheek bone, palatine bone), pathologic mandibular fracture, and osteolysis extending to the maxillary sinus floor.

Treatment of ARONJ varies with the stage of the disease [1, 2, 61]. However, regardless of the stage, the protocol must include systemic management, such as treating apical/ periodontal diseases, maintaining and improving oral health with mouthwash, and systemically administering pain medication and antibiotics. And isolated sequestra must be eliminated to promote healing of

soft tissue and to prevent further extension of ONJ. A tooth with symptoms in exposed necrotic bones is extracted, because extraction itself is unlikely to exacerbate necrosis. It is also necessary to consider therapeutic discontinuation of antiresorptive/antiangiogenic drug. The treatment of each stage is shown below (Table 2).;
Stage 0: Systemic management, including the use of pain medication and antibiotics.;
Stage 1: Use of mouthwash, rinsing and cleaning of fistula and periodontal pocket, and topical application or injection of local antimicrobial agents, education of patients, continuous follow-up.;
Stage 2: In addition to the above, symptomatic treatment with systemically administering pain medication and antibiotics. Debridement to relieve soft tissue irritation and infection control, surgical treatment such as removal of sequestra, curettage of necrotic bones, and osteotomy.;
Stage 3: In addition to the above, surgical treatment such as marginal or segmental resection of expanding necrotic bones, maintenance of nutrition with supplements and infusions.

Treatment of ARONJ should be performed in line with the following three objectives: 1. Prevention of extension of ONJ; 2. Maintenance of patient QOL by relieving symptoms including pain, pus discharge, and paresthesia, and by control of infection; 3. Patient education and routine follow-up for oral health care by dental experts [1, 2, 62].

In particular, there were many reports that surgical therapy on stage 2 is useful, outcome of MRONJ was improved [4, 29, 63]. Further study is needed on the treatment policy for Stage 1. However, from the viewpoint of maintaining QOL, it is considered important to treat stage 1 and remission without symptoms.

Management of MRONJ

Proposed risk factors for MRONJ are listed in Table 3. Among these, invasive dental treatments such as tooth extraction [4, 30, 64, 65], dental implant [4, 30, 66], or apical/periodontal surgery [4, 30, 67] are definitive local risk factors for MRONJ. It should be noted, however, that the list is not based on robust medical evidence but is a summary of published reports investigated by the Allied Committee [1, 2].

Most important approach is consultation with an appropriate dental professional when it is determined a patient would benefit from an antiresorptive/antiangiogenic drug. There is considerable support for early screening and initiation of appropriate dental care, which not only decreases the incidence of ONJ but would also accrue the benefits that all patients enjoy with optimum oral health [65, 68, 69].

Before initiation of antiresorptive/antiangiogenic drug therapy, doctors must explain to patients not only the benefits for oncology and osteoporosis, but also the

Table 1. Stage of MRONJ

Stage	Patients condition
Stage 0	Clinical symptoms were 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 were sclerotic alveolar bone, thickening and sclerosis of lamina dura, remaining tooth extraction socket.
Stage 1	Clinical symptoms were asymptomatic bone exposure/necrosis without sign of infection, or fistula in which the bone is palpable with a probe. And imaging findings were sclerotic alveolar bone, thickening and sclerosis of lamina dura, remaining tooth extraction socket.
Stage 2	Clinical symptoms were bone exposure/necrosis associated with pain, infection, fistula in which bone is palpable with a probe or at least one of the following symptoms, including bone exposure/necrosis over the alveolar bone (such as reaching the maxilla or mandibular inferior edge), which result in advanced osteolydis extending to the maxilla or mandibular inferior edge.
Stage 3	Clinical symptoms were 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 (such as 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 maxillary sinus. And imaging findings: osteosclerosis/osteolysis of the surrounding bone (cheek, palatine bone), pathologic mandibular fracture, and osteolysis extending to the maxillary sinus floor.

Table 2. Treatment of MRONJ

Stage	Treatment
Stage 0	Systemic management, including the use of pain medication and antibiotics.
Stage 1	Use of mouthwash, rinsing and cleaning of fistula and periodontal pocket, and topical application or injection of local antimicrobial agents, education of patients, continuous follow-up.
Stage 2	In addition to the above, symptomatic treatment with systemically administering pain medication and antibiotics. Debridement to relieve soft tissue irritation and infection control, surgical treatment such as removal of sequestra, curettage of necrotic bones, and osteotomy.
Stage 3	In addition to the above, surgical treatment such as marginal or segmental resection of expanding necrotic bones, maintenance of nutrition with supplements and infusions.

Table 3. Risk factor of MRONJ

Risk	
Medication	Dose Duration Route of administration Common disease
Local	Invasive dental treatment Unfitting denture and excessive bite force Poor sanitation in the oral cavity and concomitant oral disease Anatomy
Systemic	Oncology Diabetes, rheumatoid arthritis, hypocalcemia, hypoparathyroidism, osteomalacia, vitamin D deficiency, renal dialysis, anemia, and Paget's
Congenital	Single-nucleotide polymorphisms in MMP-2 and cytochrome P450-2C genes
Life-style	Smoking, drinking, and obesity
Co-administered	Anticancer agents, corticosteroids, and erythropoietin Angiogenic inhibitors Tyrosine kinase inhibitors

associated risk for MRONJ. And it is important to request that patients visit a dentist for control of oral health to prevent the occurrence of MRONJ [70]. During dental treatment in these patients, interactive communication and close cooperation between doctors and dentists is essential. It is most appropriate that physicians inform dentists of the current status, clinical courses, therapeutic history, risk factor and prognosis of the primary disease. The dentists inform doctors the oral disease and sanitation, the duration of treatment. Ideally, all dental treatments should be completed 2-3 weeks before starting antiresorptive/antiangiogenic drug therapy.

However, in the event that antiresorptive/antiangiogenic drug therapy cannot be delayed due to progression of oncology or high risk of fracture, administration of antiresorptive/antiangiogenic drug in parallel with dental treatments may be acceptable. During antiresorptive/antiangiogenic drug, patients should be instructed by doctors to adhere to routine dental visits for oral examination and management of oral care [71, 72]. Dentists should immediately inform physicians of the results of oral examinations and dental treatments, so that there is no delay in commencing therapy. It is also helpful for doctors to ask patients about the status of their oral and maxillofacial and teeth at their visits [73].

In case of invasive dental treatment, it will be careful to prevention of infection. As measures against infection prevention, there are preoperative antibiotic administration [4, 74] and would condition of complete closure [4, 64, 75]. As a kind of antibiotic, penicillin and cephem are first choice, because many of isolated bacteria on exposed bones of MRONJ are sensitive. A closed wound prevents bacterial flora from flourishing at the wound site, keeping their numbers at below 10% compared with a normal wound area [64].

For individuals who have taken an oral BP for less than four years and have no clinical risk factors, treat as usual and take notice of infection prevention [1, 2, 49]. These patients should be placed on a regular recall and observe carefully for develop of MRONJ.

For those patients who have taken an oral BP for more than four years and/or have also taken clinical risk, such as corticosteroids or antiangiogenic medications concomitantly, the prescribing doctor should be contacted to consider discontinuation of the oral BP for at least two months prior to invasive dental treatment, if systemic conditions permit. The antiresorptive should not be restarted until osseous healing has occurred. These strategies are based on reports that corticosteroid and antiangiogenic agents, in combination with antiresorptive therapy, may increase the risk of developing MRONJ and that discontinuation may mitigate this risk.

For those patients who have undergo oncology therapy intravenous BPs or Dmab, have an increased risk of developing MRONJ following invasive dental treatment and thus these procedures should be avoided if possible. Increased awareness, preventive oral management and early recognition of the signs and symptoms of MRONJ have resulted in earlier detection. Data are scant regarding the effect of discontinuing intravenous BP prior to invasive dental treatments should these be necessary. However, if MRONJ develops the oncologist may consider discontinuing antiresorptive therapy until soft tissue closure has occurred, depending on disease status.

Dmab blocks the receptor-mediated activation of osteoclasts and has no binding affinity for bone matrix, and the actions of Dmab is reversible. The half-life of Dmab is approximately 1 month [23]. Therefore, unlike BPs, the antiresorptive effects of Dmab should be mostly dissipated within 6 months of stopping the drug on osteoporosis patients. However, there are no studies to support or refute the strategy of stopping Dmab therapy in the prevention or treatment of MRONJ.

The previous studies have several limitations.; 1) unknown about the frequency of development, 2) unknown about the mechanism of development. Thus, here are few reports of high EBM for MRONJ. A large-scale prospective study will become necessary in the future.

It is possible that prevention of MRONJ. Ensuring appropriate oncology therapy and prevention of osteoporosis, along with provision of adequate dental treatment, is extremely important in patients on antiresorptive and angiogenesis inhibitor therapy; patients should not suffer the consequences of lack of collaboration between doctors and dentists. For this, it is highly desirable for dentists to have a correct understanding of the risk of development of MRONJ and the benefits of fracture prevention, as well as the mechanisms of action of antiresorptive drugs and the conditions for which they are indicated, so that they can proceed with appropriate dental treatment for individual patients without worrying too much that they might develop MRONJ. Close collaboration between doctors and dentists is the most important factor in preventing the development of MRONJ.

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No.

Conflict of Interest
No conflict of interest.

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