REVIEW
Derleme

MRONJ with Current Diagnostic and Treatment Approaches

Güncel Tanı ve Tedavi Yaklaşımlarıyla MRONJ

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ABSTRACT
Medication Related Osteonecrosis of Jaw (MRONJ) is a persistent and rare pathology that develops with progressive bone destruction and bone necrosis as a result of impaired blood supply in the mandible and maxilla. The key point to the prevention and treatment of MRONJ is screening high-risk patients predisposed to the disease to detect it at an early stage to effectively prevent the risk of progression and occurrence. Although no exposed bone is seen in clinical examination, osteonecrosis can be diagnosed early by radiographic examination. Therefore, advanced imaging techniques are important in the early diagnosis of MRONJ. There is no defined gold standard treatment in the literature and the treatment of MRONJ is often very difficult. Treatment strategies are mainly focused on minimizing the progression or formation of bone necrosis, eliminating pain, controlling infection and optimizing the patient's quality of life. American Association of Oral and Maxillofacial Surgeons (AAOMS) recommends stage-based treatment planning in MRONJ patients. In addition to the treatment methods recommended by the AAOMS, there are research showing that some adjuvant treatments have a positive effect on recovery in MRONJ patients. For example, the use of platelet-rich plasma/fibrin in addition to surgical treatment increasing the success of surgery is one of them. Alternative treatment options are low-level laser therapy, surgical debridement with laser, surgical debridement under the guidance of fluorescent staining method, use of platelet concentrates, ozone and hyperbaric oxygen therapy, pentoxifylline, alpha-tocopherol, photo-bio modulation, use of parathormone or stem cell transplantation into the lesion. In this review, we aimed to update the knowledge, attitudes and behaviors of dentists about MRONJ and to shape the approach to MRONJ with the guidance of current literature.

Key Words:
Medication-related osteonecrosis of the jaw, Diagnosis, Treatment

ÖZ
İlaca bağlı çene kemiği osteonekrozu (MRONJ), mandibula ve maksillada kanlanmanın bozulması sonucu ilerleyici kemik yıkımı ve kemik nekrozu ile gelişen, inatçı ve nadir bir patolojidir. MRONJ'un önlenmesi ve tedavisinin anahtarı, hastalığa yatkın olan yüksek riskli hastaları tarayarak ilerleme riskini ve oluşumunu etkili bir şekilde engellemek için erken aşamada saptanmasıdır. Klinik muayenede ekspoze kemik görülmediği halde radyografik inceleme ile osteonekroz erken teşhis edilebilir. Bundan dolayı ileri düzey görüntüleme teknikleri MRONJ'un erken teşhisinde önem taşımaktadır. Tedavi stratejileri esas olarak kemik nekrozunun oluşumunu veya ilerlemesini en aza indirmeye, ağrıyı ortadan kaldırmaya, enfeksiyonu kontrol etmeye ve hastanın yaşam kalitesini optimize etmeye odaklanmıştır. Amerikan Oral ve Maksillofasiyal

Cerrahi Derneği (AAOMS), MRONJ hastalarında evreye bağlı tedavi uygulamasını önermektedir. AAOMS'un önerdiği tedavi yöntemlerine ek olarak bazı yardımcı tedavilerin de iyileşmeyi olumlu etkilediğine dair araştırmalar mevcuttur. Bu derlemenin amacı, diş hekimlerinin MRONJ konusunda bilgi, tutum ve davranışlarının güncellenmesi ve MRONJ'a yaklaşımın güncel literatür rehberliğinde şekillendirilmesidir.

Anahtar Kelimeler:
İlaca bağlı çene kemiği osteonekrozu, Teşhis, Tedavi

INTRODUCTION

Bisphosphonates (BP) are the main class of drugs used for the bone diseases and are stable analogs of inorganic pyrophosphate (PPi) that bind to hydroxyapatite crystals at active bone remodeling sites (1). Bisphosphonates act by interfering with osteoclast-mediated bone resorption and disrupting intracellular signaling, therefore they are considered one of the most valid antiresorptive drugs. Since their discovery in the 1960s, they have been widely used in patients with various pathologies affecting bone tissue (such as osteoporosis and similar diseases) (1). Despite the benefits of bisphosphonates in bone metastasis and osteoporosis treatment, they also have side effects (2). The most important of these side effects is osteonecrosis of the jaw, which develops with progressive bone destruction and bone necrosis as a result of impaired blood supply caused by bisphosphonate group drugs (3). It was firstly reported by Marx et al. in 2003 that jaw bone necrosis may occur in patients using bisphosphonate group drugs (4). In the following years, it has been seen that drugs such as denosumab (RANKL inhibitor), bevacizumab (monoclonal antibody; VEGF-A inhibitor, avascular growth factor), sunitinib (tyrosine kinase inhibitor) and temsirolimus (specific mTOR inhibitor) together with BP may also cause jaw osteonecrosis (5, 6). The American Association of Oral and Maxillofacial Surgeons (AAOMS) updated the definition of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in 2014 and reported it as medication-related osteonecrosis of the jaw (MRONJ) since drugs other than bisphosphonates can induce this condition (7, 8).

As more and more antiresorptive and antiangiogenic drugs are being developed, these newer drugs appear to increase the incidence of MRONJ. In addition, studies have shown that the risk of osteonecrosis is less when these drugs are used alone, and likehood of MRONJ increases when they are used in combination with other drugs such as corticosteroids (9). According to the definition made by AAOMS in 2014, MRONJ is "in patients who have received or are receiving antiresorptive or antiangiogenic therapy before and do not have a history of radiotherapy and metastasis to the jaw area; jawbone necrosis characterized by exposed bone that persists for more than eight weeks in the maxillofacial region and can be observed through open exposure or intraoral or extraoral fistula" (7).
In this review, we aimed to update the knowledge, attitudes and behaviors of dentists about MRONJ and to shape the approach to MRONJ with the guidance of current literature.

Risk Factors for MRONJ

The risk factors for MRONJ can be considered as drug-related, local, systemic, demographic and genetic factors (10). Poor oral hygiene, inflammatory diseases such as apical periodontitis, gingival abscess, and periodontal problems are known as local factors that facilitate the development of MRONJ (11).

Many researchers have previously stated that the risk of MRONJ development increases after invasive dental treatments involving bone (tooth extraction, dental implant, apical or periodontal surgery) (12). However, it should not be forgotten that MRONJ may develop spontaneously. In addition, poorly fitting prostheses and excessive occlusal forces are also local risk factors for MRONJ (12). It is known that nitrogen-containing bisphosphonates (Alendronate, Pamidronate, Zoledronate, etc.) cause a higher rate of MRONJ formation, especially when used intravenously, compared to non-nitrogen bisphosphonates (Etidronate, Tiludronate, Clodronate, etc.) (13). In patients with malignant conditions, bisphosphonates have a higher risk of MRONJ than osteoporosis (11). The time of administration, dose, and potency of the drug are also potential factors in the MRONJ development (13). The possibility of MRONJ development increases in systemic factors that increase comorbidity such as hypocalcemia, rheumatoid arthritis, renal dialysis, anemia, hypoparathyroidism, vitamin D deficiency, osteomalacia, diabetes, and Paget's disease accompanying the patient's primary disease (14).

There are studies showing that some congenital factors for example single nucleotide polymorphism in MMP-2 and cytochrome P450-2C genes and variations in the ACE gene may be effective in the MRONJ development (15).

Many researchers have stated that demographic factors like lifestyle, smoking, obesity and alcohol use are also risk factors for MRONJ (12).

Clinical Findings and Stages of MRONJ

Presence of exposed bone (93.9% of cases) is the most significant clinical finding of MRONJ, in addition to local abscesses and soft tissue swelling, infection symptoms such as suppuration and intraoral/extraoal fistula formation can often be observed in clinical findings. If a superinfection develops in the necrotic tissue, the patient may experience severe pain, but pain is not a finding in every case. The possibility of osteoradionecrosis should also be taken into account in patients with an exposed bone who use BP and receive jaw radiation (15, 16).

The clinical findings of MRONJ can be confused with many diseases and conditions, so its differential diagnosis should be made carefully. Differential diagnosis for MRONJ include many diseases such as sinusitis, atypical neuralgia, myofascial pain, odontalgia, dental caries, periapical pathologies, fibroosseous lesions, alveolar osteitis, periodontal diseases, chronic sclerosing osteomyelitis, sarcomas, neoplastic processes of jaws or temporomandibular disorders (7). Since none of the clinical findings in question were specific to MRONJ, AAOMS conducted a study based on clinical signs and symptoms for the staging of MRONJ cases for the first time in 2007 and made the last update in 2014 (16). The MRONJ stages and treatment options updated by the AAOMS are shown in Table I (17,18).

Table I: Stages and Clinical findings and treatments of MRONJ (17, 18).

MRONJ STAGE	TREATMENT OPTIONS
At risk - No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	- No treatment needed - The patient should be informed about the risks
Stage 0 - No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes, and symptoms	- Systemic therapy including pain killers and antibiotics
Stage 1 - Exposed and necrotic bone, or fistulae that probe to bone, in patients who are asymptomatic and have no evidence of infection	- Antibacterial mouthwash - Clinical follow-up every 3 months - Patient education and review of ongoing bisphosphonate therapy in terms of indications
Stage 2 - Exposed and necrotic bone, or fistulae that probe to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	- Antibacterial mouthwashes - Oral antibiotics - Pain control - Debridement to reduce soft tissue irritation and suppress infection
Stage 3 - Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus), resulting in pathologic fracture, extraoral fistula, oral antral/oral–nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor.	- Antibacterial mouthwashes - Antibiotic therapy and pain control - Resection or surgical debridement for long-term management of pain and infection

MRONJ Radiology

In patients with bisphosphonate therapy and clinically exposed bone, there is usually no difficulty in diagnosing MRONJ. However, it is known that 30% of MRONJ cases occur without bone exposure. At this point, radiographic evaluation may take a role in the early diagnosis of stage 0 MRONJ (19).

In order to diagnose MRONJ, a careful radiological examination is required along with the clinical examination. Although no exposed bone is clinically seen, osteonecrosis can be detected at an early stage through radiographic examination (20). Although there is no imaging method approved as the gold standard in the detection of radiological findings of MRONJ, anatomical and functional imaging methods are used (21).

Anatomical Imaging

Computed tomography (CT), panoramic radiographs, magnetic resonance imaging (MRI) and cone-beam computed tomography (CBCT) are amongst the anatomical imaging methods (21).

Panoramic Radiography

In daily routine, clinical examination and radiographic evaluation are the minimum procedures to detect lesions and provide data for follow-up appointment. Especially in stage 0 MRONJ cases, early diagnosis can be made by radiographic evaluation and it will also prevent the progression of the cases to more advanced stages (22). A case of MRONJ detected at an early stage is shown in Figure 1.

In panoramic and periapical radiography, which are often used routinely, increased trabecular density, non-healing of extraction sockets, sequestra formation with radiopaque areas around the necrotic bone, thickening of the lamina dura, cortical border of the mandibular canal and maxillary sinus floor, enlargement of the periodontal ligament space, periosteal reaction and the appearance of a pathological fracture raises suspicion as a sign of osteonecrosis (23).

In the early stages of MRONJ, conventional two-dimensional (2D) radiography techniques may be insufficient. When lesions are smaller than one cm, they may appear normal on panoramic radiographs. 2D imaging techniques may be inadequate because of their lower ability to distinguish the sequestrum from healthy bones and changes in the image can only be seen when ~30-50% of bone density is lost. Due to such inadequacies, three-dimensional (3D) imaging methods such as MRI and CT are used in suspicious cases (24, 25).

Computed Tomography

Early diagnosis of osteonecrosis lesions can be achieved by evaluating the cancellous and cortical structure of the jaw bones, the entity of periosteal bone reaction and sequestrum, and the tissue integrity of adjacent structures with computerized tomography (25). Computed tomography can best determine the dimension of the lesion as it can show a larger area than the clinically observed bone exposure (26, 27). CT is superior in detecting signs of MRONJ compared to traditional methods

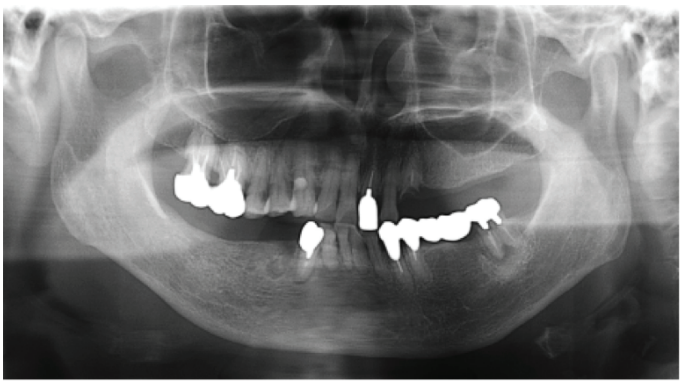

Figure 1.
A 73-year-old female presented with pain and gingival swelling at the lower right first premolar region without bone exposure; Stage 0 MRONJ was then diagnosed. She had a history of breast cancer surgery for eight years and received zoledronate for three years. A panoramic radiograph shows partial bone osteolysis at the complaint site and osteosclerosis at the right mandible. MRONJ, medication-related osteonecrosis of the jaw (22).

such as trabecular bone density change and bone sequestrum (25, 26). CT findings frequently seen in MRONJ include areas of osteosclerosis and osteolysis, irregularities and destructions at the borders of cortical bones, cortical bone perforation and sequestrum formation. The sequestrum, which is a typical finding for MRONJ, is mostly observed in the spongy trabecular bone, but can also be viewed in the cortical bone (27). The radiographic findings of the patient diagnosed with MRONJ on CT are shown in the Figure 2.

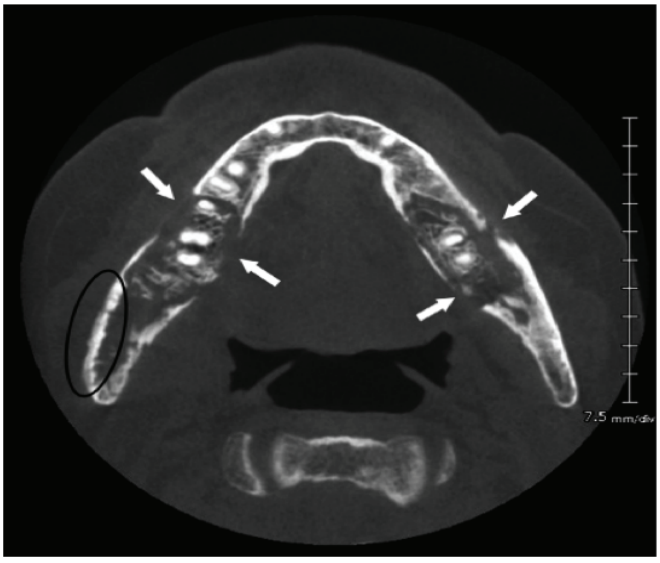

Figure 2. A 68-year-old male diagnosed with MRONJ with a history of lung cancer and developed bone metastasis. An axial CT image shows cancellous sequestra on both sides of the mandible with buccolingual cortical perforation (arrow). Periosteal reaction is also detected on the right posterior part of the buccal cortical bone (circle). MRONJ, medication-related osteonecrosis of the jaw (22).

Magnetic Resonance Imaging

It is shown that MRI is more successful in detecting early signs of stage 0 MRONJ than CBCT and CT. It also allows imaging of cervical lymphadenopathies such as submandibular and jugulodigastric lymph nodes accompanying MRONJ as soft tissues are better visualized on MRI (23). In a study, MRI was found to be able to detect early osteomyelitis of Stage 0 MRONJ which is negative on CT (28). Living bone in stage 0 MRONJ shows low intensity on T1-weighted images and high intensity on both T2-weighted images and short tau inversion recovery (STIR) images which indicate the existing inflammation (23, 26, 28). When these bones become exposed or necrotic, the density becomes hypointense at T1, T2 and STIR (19, 23, 26, 29). The necrotic bone periphery gives a high-intensity "+" image on T2 and T1 with contrast, similar to the MRONJ foci and sequestrum with a hyperintense edge. In a clinical study, early-stage MRONJ detection of 54% on panoramic radiographs was shown to offer a higher sensitivity of 92% on MRI (30, 31). The MR images of a patient diagnosed with MRONJ as a result of zoledronic acid use are shown in Figure 3.

Functional Imaging

Functional imaging methods implicate Single Photon Emission Computed Tomography (SPECT), Bone Scintigraphy and Positron Emission Tomography (PET) which can detect osteoblastic and osteoclastic activity before radiographically detected morphological changes in bone and hybrid systems (SPECT/CT, PET) which these imaging systems are combined with CT and imaging techniques such as Fluorescence Guided Bone Resection/Visibly Enhanced Lesion Coverage (VELscope) (33).

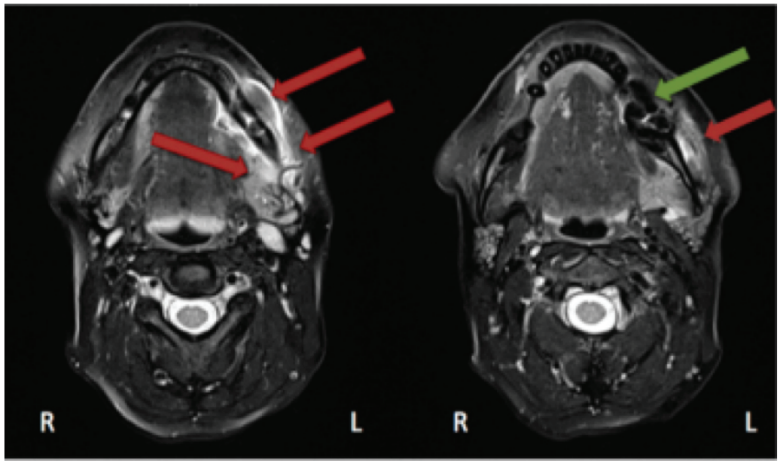

Figure 3.
Magnetic resonance imaging (Siemens, Avanto, 1.5T, Sequence: T2 tse tra) Patient: 48 years old, female, metastatic breast cancer, zoledronic acid for 2 years. Green arrow showing the MRONJ necrosis: hypointense bone marrow, red arrows showing the oedema. Pair of screenshots. AAMOS staging: stage 2 (32).

SPECT/CT

In SPECT, the distribution of radionuclide is viewed from multiple angles and in multiple two-dimensional images. A three-dimensional image is calculated from these datasets. SPECT imaging technique can be used as a hybrid SPECT/CT scanner in combination with anatomical imaging techniques. Technetium-99m methylene diphosphonate (99Tcm-MDP) or technetium-99 m-DPD (99Tcm-DPD) are constantly used nuclides to detect bone infections and do not show any major difference in pathological bone changes. The positive scintigraphy findings observed in MRONJ in many studies are consistent with histological findings, which also supports its performance in the early diagnosis of MRONJ (34). However, images created by bone scintigraphy are two-dimensional and have low anatomical resolution. Because of this negativity, in the presence of osteonecrosis, the dimensions of the lesion can not be measured with high accuracy when compared with CT and MRI. Another deficit of this technique is the insufficiency to clearly distinguish between the inflammatory and malignant stages of existing lesions (35). The SPECT/CT imaging method using Technetium is shown in the Figure 4.

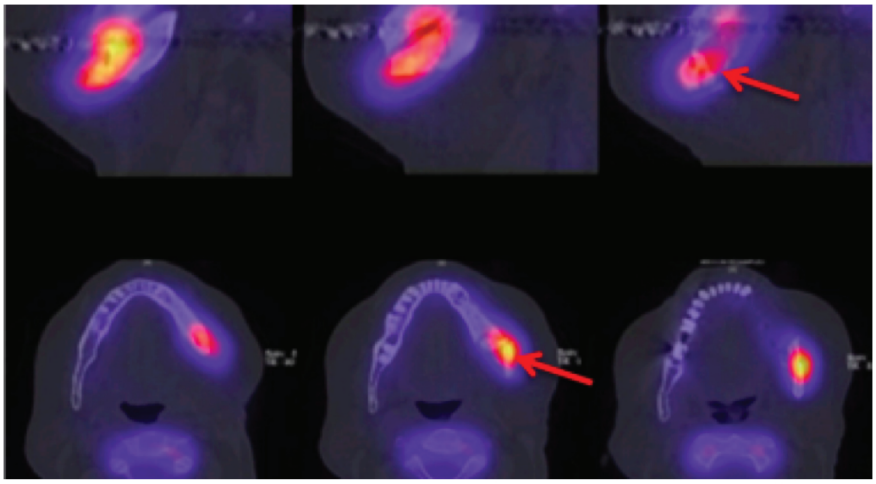

Figure 4.
Technetium-99m-3,3-diphosphono-1,2-propanodicarboxylicacid (99Tcm-DPD) SPECT/CT (Siemens, Symbia) Patient: 66 years old, male, secondary osteoporosis due to castration, alendronate. First row sagittal, second row axial view; 4.5 h after injection (bone phase). The uptake in the left mandible is clearly visible (red arrow) (32).

Positron Emission Tomography/Computerized Tomography (PET/CT)

Compared to the SPECT imaging method, the PET imaging method provides images with higher contrast and resolution. The PET/CT hybrid system consolidates anatomical imaging and functional imaging as in SPECT/CT before and compared with PET imaging, infected bone tissue can be expected to show increased glucose metabolism, an increased uptake compared to necrotic areas. Therefore, it is used to visualize suspected necrotic areas where blood flow and hypermetabolism do not occur. Abnormal mandibular development on PET scan is not unequivocally indicative of MRONJ (36).

Sodium Fluoride (NaF) is more sensitive to localize the site of osteoblastic activity than fluorodeoxyglucose (FDG). FDG acts as an analogue involved in glucose metabolism; it has high performance in detecting bone infection and determining MRONJ stages. Studies using this imaging system have shown that MRONJ cases contain both necrotic tissue and signs of inflammation. However, the common disadvantage of PET with other functional imaging methods is that inflammatory events with high metabolism and cancer types with increased metabolism have a similar appearance (37). At this point, hybrid systems (SPECT/CT, PET/CT) created by combining both SPECT and PET techniques with low specificity with CT images allows combining functional and metabolic activity with detailed radiological anatomical dimension (23, 33). The truth that the actual dimension of surgically resected MRONJ lesions were established with respect to the measurements carried out SPECT/CT images in studies conducted on this subject also displays the benefits of hybrid systems (38).

VELscope

Fluorescence-guided bone resection is a definitively defined imaging modality in integration with surgery in MRONJ. According to this method, the patient takes 100 mg of doxycycline twice a day for 10 days before surgery. Thus, living bone will have a doxycycline uptake and present a “greenish” light when illuminated by the VELscope. The fluorescence of living bone is displayed "under blue light of 400 to 460 nm" (39). There is no uptake in necrotic bone, so it does not show fluorescence. Pautke et al. concluded that bleeding of the bone during resection was not correlated with any bone fluorescence signal (40). Bone hemorrhage, suggestive of living bone, may occur in areas of cancellous bone, but no fluorescence (39). This technique may suggest a way to standardize the surgical procedure (40).

Prevention of MRONJ

The key to prevention of MRONJ is screening high-risk patients (eg, AAOMS stage 0) predisposed to the disease to detect it at an early stage to effectively prevent progression and occurrence (41). Therefore, prevention should come before treatment. Published studies have shown that local infection treatment and oral hygiene can reduce the risk of MRONJ (42). Multidisciplinary cooperations between oncologists and dentists and close follow-up play a critical role in the prevention and treatment of MRONJ. More attention should be paid to oral hygiene and periodontal health in all stages of MRONJ (43). Maintaining proper oral hygiene and using antibacterial mouthwashes may help delay the MRONJ progression (41).

Cancer patients who will receive bone marrow treatment in non-emergency circumstances should be examined in terms of oral care before starting treatment and ensure that necessary dental procedures are performed. Oncologists should inform patients about the significance of oral care before treatment and patients should be examined by a dentist to eliminate risks as much as possible. For recently diagnosed MRONJ patients, it can be determined whether bone marrow treatment should be continued or interrupted by determining the development of subsequent treatment plans (23, 33).

Treatments for dentists should be logical with a follow-up system that provides follow-up examinations. Modifiable risk factors should be assessed for patients before cancer treatment and preliminary treatments such as extraction, conservative dental and periodontal treatment, adjustment of prostheses if necessary and finally the necessity of a lifetime daily oral care commitment and encouraging reduction of risk factors (such as smoking and uncontrolled diabetes) training should be provided (44). Controllable risk factors should be minimized. During the treatment, sixth-month follow-ups should be strictly followed and if symptoms recur, a doctor should be consulted at any time. It is recommended that the dentist complete the oral examination, evaluate the condition of the soft and hard tissues in the oral cavity, continue oral education and control risk factors. The patient should be followed for 8 weeks and the outcome evaluated by the dentist (45).

Drug Holiday

Many researchers recommend stop taking medication before tooth extraction or other invasive procedures. There is insufficient information and resources to refute whether drug holiday is beneficial in patients taking antiresorptive drugs for osteoporosis. However, the AAOMS committee reviewed the modified drug vacation approach described by Damm and Jones for patients at risk and found it appropriate for patients using drugs for a long time (> four years) (46). Information on discontinuation of IV bisphosphonate therapy before surgical procedures in cancer patients is insufficient. However, if MRONJ develops, the doctor may decide to discontinue drug therapy until soft tissue healing is complete, depending on the disease condition. There is no information to support or refute the issue of discontinuing antiangiogenic drug treatment to prevent or treat MRONJ, and research on this issue is ongoing (46).

MRONJ Treatment

There is no defined gold standard treatment in the literature and MRONJ is often very difficult to treat (23, 47, 48). Treatment strategies are mainly focused on minimizing the progression or formation of bone necrosis, eliminating pain, controlling infection and optimizing the patient's quality of life (16, 23, 47, 48). The AAOMS recommends stage-based treatment planning in patients with MRONJ (Table I). No treatment is recommended other than educating the patients about what MRONJ is, necessary precautions to prevent it, and oral hygiene for patients in the risk group, (49). In cases where a mobile sequestrant develops, it should be taken regardless of the stage (16).

Medication is the primary way currently existing in the early stages of MRONJ. Considering the AAOMS' report in 2014, Stage 0 and 1 MRONJ patients may take advantage of medical treatments such as antimicrobials and systematic antibiotics (16). It can also be administered as adjuvant treatment in Stages 2 and 3 when evidence of infection emerges. Even in advanced stages requiring surgical treatment despite these recommendations, conservative medical treatment may prevail, and if the patient does not want to have surgery or the general situation of the patient does not empower surgery, conservative treatment may be a good alternative (50).

The antibiotics most commonly used for systematic drug therapy in MRONJ appear to be metronidazole, amoxicillin, penicillin, amoxicillin/clavulanate or a combination (51). In case of local antimicrobial use for the management of MRONJ, the first choice that should come to mind is chlorhexidine. Although the efficacy and extent of the application has not been fully determined, conservative treatment is a reliable method that can be applied at first and remains the most constantly tried method in the MRONJ treatment (51).

Although the AAOMS primarily recommends conservative treatment, Ristow et al. stated that the success rate was 20% in cases in which conservative treatment was preferred, while the success rate was over 85% in cases that underwent surgical treatment (52). This shows that, except for third-degree cases or well-defined sequestration, when non-operative treatment fails, operative treatment, which is a more cautious approach, should be considered. For successful surgical treatment, reducing the bacterial load with conservative methods before the operation, completely removing the necrotic bone during the surgery, removing the teeth in the necrosis area and correcting the sharp bone edges, tension-free primary closure of the wound area with a mucoperiosteal flap, laser that increases the success of surgery by disinfecting the bone, ozone, long-term antibiotic use are recommended. During surgery, the VELscope technique can also be used to distinguish between vital and necrotic bone (53). Although it has proven to be effective, some disadvantages have been reported in surgical treatment, such as worsening of symptoms after treatment, pathological fractures and loss of jaw segments. Surgical treatment has not yet been proven to treat patients in the early stages but it is a necessary modality for the treatment of more advanced MRONJ (54).

In addition to the treatment methods recommended by the AAOMS, there are research results showing that some auxiliary regenerative treatments also positively affect the recovery in MRONJ patients. Regenerative treatment choices in the treatment of MRONJ include low-dose laser therapy, surgical debridement with laser, surgical debridement under the guidance of fluorescent staining method, use of platelet concentrates, ozone and hyperbaric oxygen therapy, use of pentoxifylline, alpha-tocopherol, parathormone or stem cell transplantation into the lesion (23, 55).

Ozone therapy induces endogenous antioxidant systems and breaks the xanthine/xanthine oxidase enzyme pathway required for oxidation. It has been reported that ozone therapy increases blood circulation, erythrocyte count and hemoglobin amount, activates the mononuclear phagocytic system, contributes positively to the healing of bone defects and has antibacterial effects (56). Ozone treatment has also been reported to stimulate cell proliferation and soft tissue healing in stage 1 and 2 MRONJ (57).

Although the results of hyperbaric oxygen (HBO) are controversial, it is used in the MRONJ treatment less frequently. Some researchers have reported that HBO enhances wound healing, reduces edema and swelling, stimulates stem cell mobilization and reduces the suppression of bone regeneration caused by bisphosphonates (57, 58).

LLLT (Low-level laser therapy) has positive effects such as reducing pain, increasing wound healing and facilitating nerve regeneration. It has been stated in different studies that LLLT has been used on the basis of its biostimulant effect in MRONJ lesions (57, 59).

Pentoxifylline and α-tocopherol have been reported to help antimicrobial treatment in the early stages of MRONJ and a 74% reduction was found in the bone exposure area and symptoms in cases where they were used (57). Pentoxifylline, which is a purine-derived peripheral vasodilator substance, improves the decreased flexibility of erythrocytes, helps to increase the oxygen saturation of the tissues by decreasing the blood viscosity and increasing the flow feature, thus the microcirculation of the blood. In addition, it inhibits fibroblasts, increases collagenase activity and decreases the proinflammatory cytokines such as interleukin-12 (IL-12) and tumor necrosis factor alpha (TNF-α) (60).

Photo-bio modulation (PBM); besides its analgesic and anti-inflammatory effects, also an accelerator of tissue healing and repair (61). Cytochrome C oxidase is stimulated during PBM, resulting in increased cell proliferation, migration, differentiation, and metabolic activity (61). Since PBM enhances wound healing and modulates cell metabolism, it is considered a complementary therapy in MRONJ (62).

Another agent used in MRONJ is teriparatide. Teriparatide promotes the formation of healthy bone to replace necrotic bone by activating bone remodeling and increasing bone formation. There is also a view that teriparatide exerts its effect by suppressing sclerostin production and activating WNT signaling (63). Teriparatide has an osteoanabolic effect and has been found to encourage bone growth and healing in chronic periodontitis (64).

Mesenchymal stem cells (MSC) are well known for their ability to differentiate into tissue-forming cells for instance osteoblasts, chondrocytes and adipocytes. Due to their capacity to differentiate into osteoblasts and their immunomodulatory properties, MSCs can be used as graft material for areas of osteonecrosis (65). The efficacy of the MSC graft is related to its ability to increase TGF-β1, IL-10 and regulatory T cells (CD 4, 25) and reduce IL-6, IL-17 and C-reactive proteins (66). The limitation of MSC in the treatment of MRONJ is that it is not fully known if the primary mechanism of MSC is due to osteoblast differentiation or bone regeneration associated with immunomodulatory properties or both. In addition, MSC treatment has some detriments such as the need for additional equipment and an uncomfortable procedure. Finally, similar to other treatment modalities using grafts, MSC is difficult to implement as a single modality in the MRONJ treatment. Instead, it appears to be an adjunctive method that requires surgical treatment. Despite these limitations, MSC is taken into account as one of the most encouraging treatment modalities in combination with teriparatide due to its regenerative potential (65).

DISCUSSION

A comprehensive medical history and physical examination, along with effective radiological examinations are immensely important in the MRONJ diagnosis and planning while considering not only the presence of necrotic bone, but also other clinical signs and conventional-advanced imaging. It should be remembered that some cases of MRONJ may occur spontaneously, especially in the early stages, without the dental-periodontal diseases or any association with invasive dental procedures and it should be noted that pain may not always be present (67). The most common pathology observed in MRONJ is the emergence of non-epithelial bone, decreased number of osteocytes, more empty lacunae with increasing amounts of necrotic bone, demineralized extracellular bone matrix, denudation of bone and osteonecrosis (68).

Even though no general consensus exists on optimal treatment methods, it is noteworthy that all treatment strategies applied in practice are well-known anti-infective strategies. Conservative therapy usually comprises the use of anti-infective and oral disinfectants and long-term antibiotic therapy with temporary or even permanent cessation of antiresorptive drug therapy. Although this treatment does not usually lead to exact mucosal healing, it can lead to symptomatic relief as it can alleviate the signs of infection. It may also lead to downstaging of the disease (eg, stage 2 to 1) through reduced pain, swelling, and pus exudation (69). Surgical therapy takes place with antibiotic therapy, complete removal of necrotic bone fragments, softening of sharp-edged bones and plastic wound closure. The major intent in all these methods is to directly address the infection, remove necrotic and infected bone fragments and protect the surrounding bone from reinfection (70).

CONCLUSION

As a result, even though there is no concurrence on the preferred treatment methods, researchers agree that the most important trump card in the control of MRONJ is to prohibit the development and to detect it with advanced radiologic examinations at an early stage.

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