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MEDICATION RELATED OSTEORADIONECROSIS OF THE JAW

Dentistry

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ABSTRACT

Medication related osteoradionecrosis of the jaw is severe and progressive destruction of the jaw bone which is primarily associated with drugs such as bis-phosphonates, sunitinib and sorafenib. The pathology of the this devastating disease is unknown . the number of patients with MRONJ is significantly increasing due to wide spectrum indication of bisphosphonates and other antiresorptive drugs such as denosumab. There are various treatment and management options available which should be proceeded on the basis of extent and stages of the disease but at the same time it can be prevented by proper dental evaluation and early diagnosis and screening. This research article includes introduction, medication responsible for MRONJ, signs and symptoms, risk factors, stages of medication related osteoradionecrosis, investigations, treatment , prevention and conclusion.

KEYWORDS

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but severe debilitating condition, the exact cause for which has not yet been determined[1,2]. MRONJ is characterized by nonhealing exposed bone in patients with a history or ongoing use of an antiresorptive [bisphosphonates and denosumab] or antiangiogenic [bevacizumab, sorafenib, sunitinibe,VEGF decoy receptor] agent and no history of radiation exposure to the head and neck region[2,3].

Bisphosphonates and denosumab are predominantly used to reduce the risk of skeletal complications in patients with bone loss, resulting from long-term cancer treatment or osteoporosis, and in patients with malignant bone disease.[5,6]

Denosumab is a fully human monoclonal antibody, which has a different mode of action from that of bisphosphonates. It targets and binds to the receptor activator of nuclear factor κ-B (RANK) ligand (RANKL); in doing so it prevents the activation of RANK on the surface of osteoclasts and osteoclast precursors. Inhibition of the RANKL–RANK interaction impedes osteoclast formation, function, and survival, thereby decreasing bone resorption[4].

Medications responsible for osteoradionecrosis of jaw

ANTI RESORPTIVE DRUGS [11,12]

Bisphosphonate	Trade Name	Manufacturer	Indication for Use	Nitrogen Containing
Alendronate	Fosamax®	Merck	Osteoporosis	Yes
Risedronate	Actonel®	Warner Chilcott	Osteoporosis	Yes
Ibandronate	Boniva®	Genentech	Osteoporosis	Yes
Pamidronate	Aredia®	Novartis	Bone Metastases	Yes
Zolendronate	Zometa®	Novartis	Bone Metastases	Yes
	Reclast®	Novartis	Osteoporosis	Yes
Denosumab	Xgeva®	Amgen	Bone Metastases	No - Humanized Monoclonal Antibody
	Prolia®	Amgen	Osteoporosis	

ANTI ANGIOGENIC DRUGS [11]

Drug	Trade Name	Manufacturer	Mechanism of Action
Sunitinib	Sutent®	Pfizer	Tyrosine Kinase Inhibitor
Sorafenib	Nexavar®	Bayer	Tyrosine Kinase Inhibitor
Bevacizumab	Avastin®	Genentech	Humanized Monoclonal Antibody
Sirolimus	Rapamune®	Pfizer	Mammalian Target of Rapamycin Pathway

Signs and Symptoms

Classically, MRONJ will cause an ulcer or areas of necrotic bone for weeks, months, or even years following a tooth extraction. While the exposed, dead bone does not cause symptoms these areas often have mild pain from the inflammation of the surrounding tissues.[7] Clinical signs and symptoms associated with, but not limited to MRONJ, include:

- Jaw pain and neuropathy[8]
- Loose teeth[9]
- Mucosal swelling[9]
- Erythema
- Suppuration[17]
- Soft tissue ulceration[17]
- Trismus[9]
- Non-healing extraction sockets[9]
- Paraesthesia or numbness in the jaw[10]
- Bad breath[10]
- Exposed necrotic jaw bone[7]

RISK FACTORS[13-17]

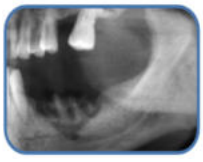
Various risk factors have been suggested to be associated with the development of ORN The local risk factors include :

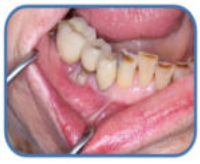
1. Tumor site and tumor stage.
2. Proximity of the tumor to bone
3. Radiation field and dose of radiation.
4. Poor oral hygiene
5. Associated trauma such as dental extraction/surgery before or after RT.
6. Systemic factors include co-morbidities, smoking and drinking alcohol, immunodeficient.
7. Other adjuvant medicines-use of gluco corticoids increases the risk when taken in the combination with the antiresorptive drugs.

STAGES

The AAOMS has defined the stages of MRONJ to describe disease presentation and to facilitate the appropriate stratification of patients[18]:

Stage 0—no clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms
Stage 1—exposed and necrotic bone/fistulae that can be probed to bone, asymptomatic, no evidence of infection
Stage 2—exposed and necrotic bone/fistulae that can be probed to bone, associated with infection
Stage 3—exposed and necrotic bone/fistulae that can be probed to bone, associated with infection and additional complications


STAGE-0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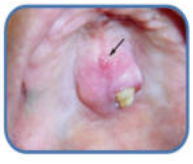
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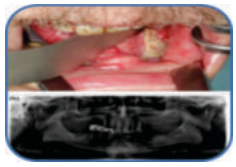
STAGE -3

Diagnosis

If osteonecrosis is suspected, panoramic and tomographic imaging may be performed to rule out other causes (e.g., cysts, impacted teeth, or metastatic disease). The radiographic signs suggestive of ONJ most often involve osteolysis consistent with bone loss. Intraoral films can

also be used to provide better detail and demonstrate more subtle bone changes. However, radiographic alterations seen in patients with ONJ treated with bisphosphonates are often subtle in earlier stages of the disease and may be difficult to detect. Initially, minimal detectable radiographic changes are observed. Over time, as surface bone breaks down, radiographs eventually show radiolucent changes[19].

Tissue biopsy should be performed only if metastatic disease is suspected. If a biopsy is warranted, microbial cultures (aerobic and anaerobic) are suggested to identify pathogens with the potential to cause secondary infections. It is important to note that Actinomyces organisms are often seen microscopically or identified upon culture[19].

TREATMENT

Conservative management

Conservative management approaches include maintaining optimal oral hygiene, eliminating active dental and periodontal diseases, and application of topical antibacterial mouth rinses and systemic antibiotic therapy, as indicated by local guidelines.[22] Such strategies may be used in cases where there is no obvious disease progression, uncontrolled pain, or discontinuation of bisphosphonate or denosumab therapy as a result of MRONJ.

Surgical management

Recent evidence suggests that surgery is effective in reducing pain in patients with MRONJ and ultimately leads its resolution. Surgery is, therefore, indicated for patients with MRONJ whose disease does not respond to or is deemed unlikely to respond to conservative approaches.[23] The following surgical principles have been proposed for the removal of necrotic bone in this patient group: "A full-thickness mucoperiosteal flap should be high and extended to reveal the entire area of exposed bone and beyond to disease-free margins; resection of the affected bone should be extended horizontally and inferiorly to reach healthy-appearing, bleeding bone; sharp edges should be smoothed; and primary soft tissue closure achieved" through appropriate mobilization and suturing to facilitate tension-free mucosal healing.[24]

Adjuvant treatment options

In addition to the established conservative and surgical treatment options, several adjuvant treatments for MRONJ have been investigated, including laser-assisted surgical debridement/low-level laser therapy and the application of ozone oil or platelet-rich plasma/platelet-derived growth factor to the surgical wound. However, it should be noted that these techniques have yielded conflicting results and have not yet been assessed in prospective controlled clinical trials[25].

PREVENTION

Because ONJ treatment is regarded as being difficult, efforts are focused on the prevention of ONJ with a multidisciplinary approach. Before starting antiresorptive therapy, patients should have a full oral examination with oral hygiene instructions, and educated about the chance of developing ONJ[26], the signs and symptoms, and the risk factors for developing ONJ . Any necessary dental treatment, especially invasive procedures such as extractions, should be done before antiresorptive therapy. Careful dental preparation and oral hygiene instructions significantly reduce the risk of MRONJ[27]. The prescribing provider should be contacted before dentoalveolar surgery in cases on antiresorptive therapy for more than three years to discontinue antiresorptive medication for two months before oral surgery (i.e., a drug holiday). Intravenous antiresorptive therapy and ongoing cancer therapy are absolute contraindications for any dental surgery including implant placement[28] . The application of autologous platelet concentrates could be helpful in the prevention of MRONJ due to their local immunomodulatory properties and possible angiogenesis acceleration[29] .

CONCLUSION

Although the benefits of treatment with bisphosphonates or denosumab are clearly established, MRONJ has emerged as an important safety consideration. To optimize the use of these agents in practice and to ensure appropriate focus on the risk of MRONJ, good collaboration is required among dentists, physicians, oral oncologists, OMFSs, and other health care professionals involved in a patient's care. Although it is important to be aware of MRONJ and understand which patients are most likely to be affected, dentists should also be aware of the educational materials available to them and not overestimate the risk of this condition and restrict dental care unnecessarily. Moreover, lack of communication among care providers may result in misunderstandings regarding the reasons for, and the risks of, treatment with bisphosphonates or denosumab. Such misunderstandings may lead to conflicting information being given to the patient. This can ultimately jeopardize the patient's trust and adherence to the proposed treatment, leading to inferior health outcomes.

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