Medication related osteonecrosis of jaw – A medical oncologist's perspective

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Abstract
Medication related osteonecrosis of jaw (MRONJ) is a rare iatrogenic disease. Cancer therapeutics is advancing exponentially and apart from a major emphasis on quality of life (QoL) in metastatic patients, now we are foreseeing increased longevity. This necessitates the rising need of betterment of supportive care modalities and looking into the rare complications of therapy. Bisphosphonates (BPs) and Denosumab, the anti-resorptive agents (ARAs) used commonly by medical oncologists in cancers with bone metastases and less commonly in prevention or treatment of osteoporosis, are implicated in the etiology of MRONJ. Many a times, it goes undetected, underdiagnosed and untreated due to lack of awareness, low index of suspicion and paucity of understanding of this disorder amongst medical oncology fraternity. A high index of suspicion is a cornerstone of timely diagnosis and therapeutic action. A regular collaboration between treating oncologist and dentist is of utmost importance.

Introduction
MRONJ is a rare skeletal disorder affecting the jaw bone, mandible more commonly than maxillae. It occurs in the patients on long term bisphosphonates, denosumab and less commonly antiangiogenic agents. Being a very rare disease, it is hardly ever suspected initially. On the contrary, anti-resorptive agents are phenomenally used in oncology. Hence, it is infrequently seen in rare patients, albeit at advanced stages. Cancer therapeutics is advancing at a fast pace exploring the paradigm of increasing quantity of life. In this scenario, cancer supportive care has to match its steps to provide a better quality of life throughout. The current role of bone-modifying agents (BMAs) is primarily improving the QoL. As the survival of metastatic patients treated with BMAs increases, the incidence of MRONJ is bound to increase. Hence, better understanding of the molecular pathophysiology, clinical patterns and management of MRONJ is the need of the hour.

Background
MRONJ, is a rare but serious adverse effect of ARAs, which are widely used in oncology, and less commonly used in certain non-oncological diseases. It was first described in 2002.[1] Cancer patients with bone metastases require more frequent administration of ARAs than osteoporosis and other diseases, leading to a substantially higher risk for ONJ.[2-5] ONJ was earlier known as BRONJ (bisphosphonate-related ONJ), Now being increasingly recognised to be associated with other agents like denosumab and antiangiogenic agents, it is now recommended by American Association of Oral and Maxillofacial Surgeons (AAOMS) as "MRONJ".[6]

Definition — AAOMS, position paper 2014[6]

"Patients may be considered to have MRONJ if the following characteristics are present:

1. Current or previous treatment with antiresorptive or antiangiogenic agents
2. Exposed or necrotic bone in the maxillofacial region that has persisted for more than eight weeks
3. No history of radiation therapy to or obvious metastatic disease in the jawbones"

Common Indications of ARAs in Oncology: In a cancer patient, bone metastases can lead to multiple skeletal related events (SREs) viz local pain, fracture, hypercalcaemia or compressive myelopathy.[7,8] BPs and denosumab, are BMAs, which significantly reduce the morbidity due to SREs in metastatic solid organ cancers, through octeoclast inhibition. They are also frequently used in multiple myeloma, and less commonly for hormone therapies related bone loss. In metastatic breast cancer, BPs has been shown to reduce the risk of SREs by 14%. Apart from improvement in QoL, median time to SREs is also delayed. Overall survival remains the same.[9]

Zoledronic acid

Bone metastases from solid tumors: IV: 4 mg q3-4 weeks[10]

Hypercalcemia of malignancy: IV: 4 mg as a single dose. Can be repeated after 7 days.

Multiple myeloma osteolytic lesions: IV: 4 mg q3-4 weeks[10]

Osteoporosis treatment: IV: 5 mg once a year

Osteoporosis, prevention: IV: 5 mg q2 years

Prevention of bone loss with androgen deprivation therapy in prostate cancer: 4 mg q12 months,[11] breast cancer: 4 mg q6 months for 5 years[12]

Denosumab

Bone metastases from solid tumors: 120 mg q4 weeks

Giant cell tumor of bone: 120 mg q4 weeks; during the first month, give an additional 120 mg on days 8 and 15[13,14]

Hypercalcemia of malignancy: 120 mg q4 weeks; during the first month, give an additional 120 mg on days 8 and 15[15]
Multiple myeloma: 120 mg q4 weeks[16]
Osteoporosis/bone loss:
Treatment of androgen deprivation-induced bone loss in men with prostate cancer: 60 mg as a single dose, q6m[17]
Treatment of aromatase inhibitor-induced bone loss in women with breast cancer: 60 mg as a single dose, q6m[18]
Treatment of osteoporosis in men or in postmenopausal women: SubQ: 60 mg as a single dose, q6m

Choosing between Bisphosphonates vs Denosumab: As a general rule, BMAs are recommended for all cancer patients with bone metastases, with a few exceptions, viz. Oligometastates and limited expected survival. A meta-analysis of three phase III randomised trials comparing zoledronic acid and denosumab in bone metastases proved denosumab to be superior to zoledronic acid in risk reduction of a first SRE (hazard ratio [HR] 0.83, 95% CI 0.76-0.90) and in delaying the occurrence of a first SRE or malignancy related hypercalcemia (median 26.6 vs 19.4 months).[19] OS and PFS were similar with both agents. Similarly, a Cochrane analysis of three trials on breast cancer; denosumab treated women experienced 22% less SREs compared with bisphosphonate treated women (risk ratio [RR] 0.78, 95% CI 0.72-0.85).[20] Denosumab is easier and quicker to administer, as it is SC injection. It does not cause acute phase reactions. Hypocalcemia is more common with denosumab. Zoledronic acid requires renal modification. MRONJ occurs at similar rate. Hence, health related-QoL is better with denosumab.[21] In cancers other than breast and prostate, denosumab delays the onset of pain by 4 months.[22]

Comparative MoA: Bisphosphonates comprise 2 classes; non-nitrogen containing (etidronate, tiludronate, clodronate) and nitrogen conataining (zoledronate, pamidronate, ibandrinate, alendronate, risedronate). The latter are more potent osteoclast inhibitors. Apart from reducing bone resorption, they also augment mineralization, cause osteoclasts apoptosis, and interfere with their maturation and differentiation. Other lesser defined mechanisms include influence on macrophages, osteoblasts, tumor cells and gamma delta T cells, altering tumor microenvironment.[23,24] Denosumab is a monoclonal antibody inhibiting the RANKL (receptor activator of nuclear factor kappa B ligand), a key component in the pathway for osteoclast development and activation.

Deciding the Frequency of Administration: The recommended dosing for zoledronic acid is 4 mg IV 3-4 weekly. Less frequent dosing (q12 weekly) is also proven to be equally effective in metastatic breast cancer and CRPC.[25] The approved dosing for denosumab for SREs prevention is 120 mg SC 4 weekly. 12 wkly dosing of denosumab is not yet approved.

Incidence of ONJ: MRONJ occurs more commonly in cancer patients than in osteoporosis patients. In the former, with oral/IV nitrogen-containing BPs, MRONJ incidence ranges from 0.001 to 0.01%, paralleling or slightly higher than the general population (0.001%). For denosumab, the incidence is 0–30.2/100,000 patients per year.[26] Incidence of MRONJ in cancer patients with bone metastases treated monthly is same for BPs, and RANKL inhibitor therapy (1.3% on zoldronic acid and 1.9% on denosumab over 3 years, p=0.08). Median time to onset is 15-16 months.[27] Longer exposure increases the cumulative incidence (0.7-1.4% during the first year vs 2-3.4% with continued exposure beyond one year.[28-31] As compared to non-nitogenous compounds (0-0.19%), nitrogenous ones appear to confer 50-100 fold higher risk of ONJ.[32] It probably implies that increased efficacy of nitrogen containing BPs comes at the cost of increased adverse events. Most of the cases are preceded by major dental problems (dental extraction 63%, jaw pain 82%, and a dental infection 48%), indicating the need for a thorugh dental history and examination, preferably by a dentist.

Predicting ONJ Risk Vs Necessity of Antiresorptive Agents: The diagnosis of a metastatic malignancy is a devastating event for a patient and the family. There is an urgent need/ expectation to provide maximum care and comfort at the earliest with whatever modalities available. Eventually, being a rare condition, ONJ, per se, comes much down below in the considerations to decide therapy. As a matter of fact, except for a few cancers with bone metastases, e.g, breast and prostate cancer, most of the solid organ cancers had expected median survival of only 2-3 years, with conventional treatment modalities. With the advent of newer modalities including targeted therapies and immuno-oncological drugs, the expected survival and QoL are improving. Hence, the ONJ risk needs to be thoroughly weighed against the choice of BMA. Nonetheless, we routinely ask for the history of previous BMAs, history of major dental procedures, any major dental ailments or any planned dental procedure in the near future. We perform basic dental and oral examination and in case of any obvious or apparent dental issue, an opinion of dental surgeon a dental surgeon is solicited.

Selecting High-Risk Cases: High risk factors can be local or systemic. In the local risk factors tooth extraction, dentoalveolar surgery, poor oral hygiene, jaw infections, dental implants and dental caries are to be looked for. In the systemic risk factors, apart from type, number and duration of BMA administration, anti-angiogenics, monoclonal antibodies, steroids, chemotherapy, RT, smoking, drinking, obesity, rheumatoid arthritis, hypocalcemia, hypoparathyroidism, osteomalacia, vitamin D deficiency, renal dialysis, anemia, and Paget's disease of bone and uncontrolled diabetes are important.[33,34]

Suspecting ONJ: The diagnosis of ONJ requires a very high risk of suspicion. Exposed or necrotic areas(symptomatic or asymptomatic) of jaw bone, persisting for weeks, months, or even years, are the hallmark of MRONJ.[35] Symptoms occur when there is accompanying soft tissue inflammation. Early warning clinical features include prolonged painful jaw, loosening of teeth, non-healing tooth extraction site, bony enlargement, gum swelling, focal erythema and non-healing ulceration.[35-37] Secondary infection can cause focal necrosis of surrounding soft tissue leading to fistula/e (Intraoral or extraoral). Inflammatory and necrotic process may damage/infiltrate nearby neurovascular structures causing neuralgia or bleeding. Mandible is affected two times more often than maxillae.[32,38]

Diagnosis of ONJ: MRONJ is a clinco-radiological diagnosis. The key to success lies in detection at the earliest stage possible. Any previous imaging studies must be retrieved, whenever feasible for comparison. There are no specific imaging features diagnostic of MRONJ. Various radiographic modalities used are panoramic X-rays, cone-beam computed tomography (CT), or magnetic resonance imaging. Early stages are more difficult to diagnose as the changes, viz nonhealing dental extraction sites, periapical fluid shadows and loosening of teeth, are not disease specific.[39] CT better delineates focal bone sclerosis, mineralization, periosteal reaction and sequestra.[35] Radionuclide bone scan is potentially useful in demonstrating early inflammatory changes suggestive of degenerating bone.[40,41]

Differential Diagnosis: MRONJ may mimic jaw bone metastases, chronic alveolar osteitis, chronic maxillary sinusitis, gingivitis/ periodontitis, caries, periapical inflammation, osteosarcoma, sclerosing osteomyelitis, and temporomandibular joint dysfunction. Osteoradionecrosis is the term used for similar phenomenon noticed in patients exposed to local radiation.

Staging[34]:

"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

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.

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 maxillary sinus

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 ONJ: Treating ONJ is the most challenging part. There are no evidence based guidelines. Prevention is always easier than cure. As per AAOMS guidelines, in patients at risk of MRONJ, observation and education is recommended. In stage 0, conservative management with analgesics and antibiotics is appropriate. Stopping the BMAs needs to be considered at stage 1, alongwith application of mouth-rinses. Surgical debridement is the mainstay in stage 2 and 3, apart from use of long term antibiotics and other supportive measures.[26]

Role of Oncologist after the Diagnosis of MRONJ: A cancer with multiple bone metastases is an incurable scenario. Hence, every medical decision is intended to preserve / improve the QoL. For a local pathology like MRONJ, cancer treatment should not be stopped, if patient is otherwise fit. Hence, cancer and MRONJ treatment will go hand-in-hand. Unless dental/ maxillo-facial surgery is not planned, most of the time the patient will be under the care of a medical oncologist. The combined goals of treatment shall be continuation of oncologic treatment and preservation of QoL. Patient shall need reassurance, control of pain/ secondary infection, and prevention of extension and development of new areas of necrosis. These can be

achieved through collaboration with the dental surgeon. He may advise maintaining optimal oral hygiene, administration of systemic antibiotics, mouth rinses with chlorexidine and frequent dental inspection.

Prevention of MRONJ: Starting a BMAs is never an emergency except for severe hypercalcaemia of malignancy. Hence, baseline dental and oral examination prior to initiation of BMAs must be considered.

1. Required dental procedures should be performed prior initiation of BMA.
2. Maintain appropriate oral hygiene
3. Avoid dental extraction or surgery to the jaw when possible, during BMA administration
4. When unavoidable application of minimally invasive surgery is preferred
5. Frequent monitoring by a dental care provider during and after BMA administration
6. Ensuring drug holiday around the procedures

Drug Holiday: Drug holiday in BMAs means withholding the drug for a sufficient safe time before and after a dental procedure to allow complete healing, minimising the risk of MRONJ and without compromising the benefits of BMA therapy. All three goals may not be completely fulfilled and moreover, we have incomplete knowledge of the subtle nuances of pathophysiology of MRONJ. Apparently, the concept of drug holiday holds more relevance in the context of bone metastases, where the administration is more frequent. BPs are deposited on the osteoclast-bone matrix interface for long time,[42] a short-term withdrawl is unlikely to prevent MRONJ. Logically, it may be worthwhile for denosumab, as it causes reversible osteoclast inhibition. Ideally, all dental treatments should be completed 2 weeks before starting antiresorptive treatment The American Dental Association suggests that the incidence of MRONJ in patients with osteoporosis is at most 0.1%, and suggests that the benefits of BMAs for fracture prevention outweigh the risks for MRONJ. Discontinuation of BMAs is unlikely to reduce the risk of ARONJ, but will increase the negative effects such as increased fracture occurrence.[43] AAOMS recommends that, for patients receiving ARAs for longer than 4 years and who have low fracture risk but potentially high risk for MRONJ, discontinuation of BMAs for approximately 2 months before invasive dental treatment should be considered. If fracture risk or bone metastasis is well-controlled, resumption of BMAs is recommended approximately 2 months after the invasive dental procudure, when the damaged alveolar bones are expected to have healed.[44]

Max duration of BMAs: Minimum duration necessary for administration of BMAs is 6 months to obtain a significant fracture risk reduction, in cancer patients with bone metastases. Treatment can be continued indefinitely in the absence of excessive toxicity.[25,45] Their analgesic effect makes these useful even in hospice setting.[46]

Prognosis: 60% the MRONJ patients can be adequately treated with oral rinses and antibiotics, with 40% requiring oral surgeries including sequestrectomy, debridement, or extraction. The culprit drug must preferably be withheld at confirmation of the diagnosis. Reinitiation may be considered on complete mucosal recovery. Complete resolution rate is 40% for denosumab compared to 30% for zoldronic acid.[32]

Does this Affect Cancer Survival: Per se, no patient of cancer will generally die due to MRONJ. Nevertheless, studies have compared the survival of patients on BMAs with and without MRONJ. In a matched non-randomised comparative cohort study on patient databases in Denmark, among the matched patients, MRONJ patients experienced reduced survival, with an adjusted mortality rate ratio of 1.31(95% CI: 1.01-1.71). ONJ may be a marker of advanced disease or of survival-related lifestyle characteristics.[47]

Oncologist-dentist Partnership: Rarity of the disease and incomplete understanding of the nature, etiology, pathophysiology, treatment and course of the disease necessitates the need of a better understanding, collaboration and frequent interaction among dentists and medical oncologists.

Future Directions: Although first case of MRONJ was reported in 2002, still our understanding of its epidemiology and pathophysiology is limited. Despite having a different mechanism of action, the newer anti-resorptive agent, denosumab, has also shown the same incidence of MRONJ. In this molecular era, we shall undoubtedly invent newer antiresorptive agents, with distinct pharmacological properties, and possibly less occurrence of ONJ. Nevertheless, we need to have better understanding of the risk factors and pathogenesis of ARONJ are crucial. Standard guidelines for stopping, withholding and restarting BMAS in cases of any planned dentalprocedure and MRONJ are yet to evolve. Prior to inititation and during continuation of anti-resorptive therapy, Vitamin D and serum calcium levels ought to be carefully maintained. Both categories of BMAs cause hypocalcaemia (higher with denosumab). It may be worthwhile to look into the association between prolonged hypocalcaemia and MRONJ, for which no major studies are available, although it may not be ethically possible. The unresolved problem of MRONJ invites closer and frequent multilevel collaboration between medical oncologist and dentists to achieve greater prevention and better oncological care.

Conclusion

MRONJ is a rare, non-fatal and probably thus underexplored realm. It's complicated pathophysiology undermines the need of better patient education and dental evaluation at the beginning of BMAs. As the advent of better cancer therapies are going to expand

the therapeutic armamentarium and eventually improving the quality and quantity of life, medical oncology fraternity also needs to sensitize and update itself regarding this entity.

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