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Role of bisphosphonate in dental and clinical practice- A review

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Abstract

Bisphosphonates (BPs) have utility across a wide range of disciplines including endocrinology, oncology, orthopaedics, and dentistry owing to their ability to inhibit osteoclasts. However, the most dreadful adverse effect of inhibition of bone resorption is the development of avascular necrosis termed bisphosphonate-related osteonecrosis of the jaws (BRONJ). The present article aims to describe various aspects of BRONJ while emphasizing its clinical presentation and pathophysiology. Appropriate preventive measures must be taken with regard to the oral healthcare of the patients on BP therapy to prevent the development of BRONJ. Should the disease develop, the clinicians must be able to formulate an appropriate treatment plan while minimizing the damage caused by the disease process. In this regard, the present review would serve to guide the clinicians in taking a prompt decision on how to proceed with the management of patients with BRONJ.

Keywords: Osteonecrosis; Medications; Resorption; Osteoclasts.

Introduction

Bisphosphonates (BPs) are synthetic analogues of pyrophosphate, a normal constituent of the bone matrix. BPs inhibit bone resorption by suppressing the activation of osteoclasts and inducing their apoptosis.[1] The drugs inhibit bone resorption and thus impart a hypocalcemic effect. Because of their inhibitory effect on osteoclastic resorption, BPs have found their utility across a wide range of disciplines including endocrinology, oncology, orthopaedics, and dentistry.[2]

While their efficacy has been established across multiple studies, certain adverse effects have given rise to reluctance on the part of clinicians to use BPs. The most dreadful adverse effect of BPs is related to its primary mechanism of inhibition of osteoclasts which results in avascular necrosis of the jawbones termed 'Bisphosphonate-related osteonecrosis of the jaw' (BRONJ).[3] Osteonecrosis refers to the bone's death due to impaired blood supply to the affected areas. The non-viable bone then becomes exposed to the bacteria-rich oral environment, resulting in pain and infection. The

first cases of BRONJ were reported in 2003 in the United States and reports of thousands of similar cases flurried in the subsequent years.[4]

While incidence rates ranging from 0.01% to 0.06% have been reported in the literature, the exact incidence of BRONJ is not known.[5] This is because similar osteonecrosis of the jaws occurs in relation to other medications such as denosumab, bevacizumab, cabozantinib, and sunitinib, all of which are collectively termed as medication-related osteonecrosis of the jaw (MRONJ).[6]

The present article aims to describe various aspects of BRONJ while emphasizing its clinical presentation and pathophysiology.

Bisphosphonates

BPs are routinely prescribed for commonly prescribed for bone diseases such as osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, osteolytic bone metastases in the context of solid tumours and osteolytic lesions of multiple myeloma.[7] While BPs do not have a significant effect on the neoplastic cells *per se*, they have been implicated in having a positive effect on the quality of life for patients having advanced stages of cancer with skeletal involvement. Neoplastic cells elaborate receptor activator nuclear Kappa-β ligand (RANKL), which normally activate the receptor activator nuclear Kappa-β (RANK) receptors on the osteoclast cell membrane.[8] Activation of these receptors signals the osteoclasts to actively resorb bone and create resorption cavities into which the neoplastic cells proliferate. BPs inhibit this resorption and the ensuing infiltration of cells, thereby limiting the local extension of neoplasm. Similar prevention of bone resorption is useful in osteoporosis which commonly occurs in women after menopause. This results in a more mineralized and stronger bone which, however, becomes brittle and keeps accumulating because of the absence of resorption over a period of years.

BPs can be broadly classified into two types based on their chemical composition into nitrogen-containing and non-nitrogen-containing, with subgroups comprising modes of administration, that are, oral or intravenous.[9-11] The nitrogen-containing BPs inhibit farnesyl pyrophosphate synthesis and block the mevalonate pathway in the osteoclasts.[10] Some examples of nitrogen-containing BPs include alendronate, risedronate, pamidronate, ibandronate, and zoledronate. They are more potent inhibitors of osteoclastic activity, endothelial cell proliferation, adhesion and migration, and angiogenesis. The non-nitrogen BPs interfere with the intracellular metabolic enzymes of the osteoclasts by forming cytotoxic metabolites subsequently causing their death.[11] Nitrogen-containing BPs are poorly absorbed in the gastrointestinal system and are, thus, administered preferably by intravenous route.

Pathophysiology of BRONJ

BPs impair the function and survival of the osteoclasts, and consequently the bone remodelling process. Osteocytes have a life span of 150 days, after which osteoclasts resorb the mineral matrix of bone and release bone morphogenic protein (BMP) and insulin-like growth factor, which in turn induce local stem cells to differentiate into osteoblasts and form new bone matrix.[12] In this manner, resorption always precedes bone formation. In the absence of resorption, the impending BMP and growth factors are not released and new bone does not get formed. The cycle of bone resorption and deposition in the regular remodelling process gets disrupted.

The alveolar bones are constantly subjected to stresses and microtrauma by functional and parafunctional actions. Under normal conditions, these microtraumas

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heal by continuous remodelling of the bone.[13] In patients under BP therapy, the old bone is retained beyond its normal lifespan which leads to the accumulation of microdamage and reduction in the mechanical properties of the bone. Osteoblasts continue to deposit new bone despite the retention of older, damaged bone. BPs also possess anti-angiogenic properties which lead to a compromised blood supply to the maxillofacial bones during repair.[14] Because the capillary network fails to maintain for such long periods of time, avascular necrosis of the bone occurs. The process of the pathogenesis of BRONJ is depicted in Figure 1.

BPs may also have a toxic effect on cells other than osteoclasts such as epithelial cells and endothelial cells which could secondarily lead to bone exposure and impaired healing as a direct effect of the drug rather than an aggravating invasive surgical procedure.[14] Microbial infections may further lead to the degradation of the bone by liberating destructive enzymes and endotoxins. The lowered pH because of pus and cytokines released during infection further accentuates the release of BPs and their subsequent actions.[15] Recent studies have demonstrated that single nucleotide polymorphisms in several genes are responsible for a genetic predisposition to develop.[16]

The exact pathogenesis of BRONJ may not be the same in every case; two major theories have been suggested with reference to the beginning and spread of the pathological process.[17] First is the 'inside-out' theory which states that suppression of osteoclastic activity and bone turnover occurs first with a concomitant spread of micro-damage. Local accumulation of dead bone occurs which subsequently gets exposed, with or without additional infection. The other theory i.e. 'the outside-in' theory states that ingress of bacteria and local infection occurs first through a breach in the mucosal integrity.[17] Compromised vascular supply and defective remodelling occur later which leads to bone necrosis and accumulation of the sequestrate.[14] In this theory, bone exposure occurs chronologically much later in the disease process. Either of the theories may not be entirely applicable to every case of BRONJ; While it is virtually impossible to clinically determine which of the two mechanisms has occurred, a combination of both can be rationally expected.

Clinicodemographic characteristics of BRONJ

BRONJ occurs in about 10% of patients receiving bisphosphonate therapy. It has been reported that about 40% of patients with BRONJ were those taking BPs by oral route, while higher incidence has been generally reported in patients with intravenous BP administration.[18] BRONJ generally occurs in females and individuals above 60 years of age.[19] The higher prevalence in females may be attributed to the higher prevalence of osteoporosis, osteopenia, and breast cancer.

The pathological process typically begins in the alveolar bone with a higher propensity to occur in the maxilla in almost two-thirds of cases.[18] Extraction sockets, tori and mylohyoid ridge constitute the most common sites of occurrence. The typical presentation of the lesion is an area of exposed alveolar bone that occurs spontaneously or following invasive dental surgical procedures such as extraction, apicoectomy, periodontal surgery or implant placement. About 69% of cases have been reported to occur after a tooth extraction or other dentoalveolar surgery.[20] The lesion does not heal for over a period of 6 to 8 weeks and is usually refractory to conventional treatments such as debridement, antibiotics, and hyperbaric oxygen therapy.

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Although the systemic administration of BPs affects the function of osteoclasts throughout the entire skeletal system, BRONJ exclusively occurs in the jawbones. The differences between the developmental mechanisms of jaw bones and long bones contribute to the site-specific occurrence of BRONJ. The maxilla and mandible develop via intramembranous bone formation while long bones develop via endochondral ossification. Thus, significant differences exist in their anatomy, density, and the proportion of cortical versus cancellous bone and marrow spaces.[21] Mandible relatively comprises greater amounts of type I, III, and V collagen and lower hydroxylysine of collagen as compared to the long bones. Such features may contribute to a higher rate of bone turnover in jaw bones, which is thought to be necessary to meet the mechanical needs of the mandible. BP uptake into bone is in direct proportion to the local rate of bone turnover and thus, accounts for the higher incidence in the jaw.[18,21]

The size of the lesion gradually increases from a localized involvement of a few millimetres to extensively involving larger areas of the alveolar bone. Pain, swelling, tooth mobility, and pus discharge through sinus tracts are some of the symptoms commonly reported by the patients; occasionally a fistulous tract may develop in severe cases. About 80% of patients with BRONJ complain of painful lesions.[22] The pain occurs as a result of exposure to underlying nerves and osseous tissue and is described by the patients to be so severe that it interferes with eating, brushing or even speaking. The exposed bone having a ragged surface or edges may ulcerate the mucosal tissues that come in contact during function.[23] Seldom the patient may be asymptomatic until provoked by some aggravating factor such as trauma or infection.

Patients at risk for or with established BRONJ may present with additional clinical conditions that must be differentiated from BRONJ. These commonly include dry sockets, periapical lesions, gingivitis/periodontitis, sinusitis, and TMJ disorders. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has defined certain criteria for diagnosis of BRONJ which include ongoing or history of previous treatment with BP, exposed and necrotic bone in the maxillofacial region that has persisted for more than 8 weeks, negative history of cancer at the site and radiation therapy to the jaws.[24]

The clinical staging system for BRONJ proposed by AAOMS in 2009 for patients on BP therapy is tabulated in Table 1.[25] Nevertheless, the treatment protocol has to be tailored after due consideration of clinicodemographic, pathological, and economical factors for each case individually.

Since all the patients on BP therapy do not develop BRONJ, it would only be rational to believe that several co-factors may play a role in predisposing an individual towards its development. For instance, the risk of developing BRONJ associated with oral bisphosphonates, while exceedingly small, appears to increase when the duration of therapy exceeds 3 years.

The AAOMS recently grouped the risk factors for the development of BRONJ into drug-related, local, demographic and systematic, genetic, and preventive.[26] Besides preventive factors that are discussed in the subsequent text, the other factors are summarized in Figure 2.

Treatment strategies

A meticulous intraoral examination to identify grossly carious teeth, gingival and periodontal conditions, and the need for invasive surgical procedures must be carried out prior to the commencement of BP therapy. Such

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preventive dental treatment has been demonstrated to reduce the risk of developing BRONJ among patients with malignancy treated with IV bisphosphonates. Although not absolutely contraindicated, elective dental procedures must be deferred until much is necessary in patients under BP therapy.[27] If the systemic condition allows, the BP therapy may be stopped for 3 months to 3 years following invasive oral treatment procedures which have been shown to improve the treatment outcome in patients with BRONJ. Besides cessation of habit, much of the treatment in incipient or mild cases focuses on palliative care which comprises pain and infection control.

The treatment strategies can be classified into three categories depending on the extent of the disease and the corresponding aggressiveness of the treatment required (Figure 3).[26] The first category comprises 'conservative' modalities that aim to subside the infection and provide optimal local conditions for wound healing with no or minimal surgical intervention. These include prescription of oral antibiotics and mouth rinses. The AAOMS has recommended the use of 0.12% chlorhexidine to prevent secondary infections or minimize those already established in patients with BRONJ.[25]

A tailored dosage of non-steroidal anti-inflammatory drugs or acetaminophen has been recommended for pain management.[25,26] Empirical treatment with penicillin has been recommended for necrotic bone infections by the AAOMS. Doxycycline, erythromycin, fluoroquinolones, metronidazole, or clindamycin may be used in cases of allergy to penicillin.[28] Antibiotic therapy should be streamlined at once after obtaining the results of the culture sensitivity tests. Local debridement of necrotic bone, curettage and rinsing with 1% povidone-iodine can vastly benefit in relieving local infection and pain.

The second category comprises 'surgical' treatment modalities that aim to remove the necrotic tissues and accelerate wound closure. Surgical treatment is required in relatively advanced cases wherein non-invasive modalities would not suffice and a more radical cure is required.[29] Sequential removal of the affected bone is considered an appropriate measure in localized cases. In extensive cases, surgical resection includes partial maxillectomy or segmental mandibulectomy followed by replacement with the fibula and tissue flaps or jaw prostheses. Surgical techniques are effective in providing a radical cure and long-term palliation.

The third category comprises 'add-on' therapeutic tools which include adjunctive, relatively newer modalities such as hyperbaric oxygen therapy, fluorescence-guided bone resection, low-intensity laser therapy, ozone therapy, use of platelet-rich plasma.[28] Recently, the use of growth and differentiation factors as well as transplantation of intra-lesional autologous bone marrow stem cells have been attempted with reasonable success.[29] Hyperbaric oxygen therapy increases bone turnover by stimulating osteoclast differentiation, activity and viability, although some cases may be refractive.

Conclusion

While bisphosphonates are a boon to many patients suffering from cancers and other serious pathologies of bone, their most dreadful adverse effect, BRONJ, cannot be trifled with. Appropriate preventive measures must be taken with regard to the oral healthcare of the patients on BP therapy to prevent the development of BRONJ. Should the disease develop, the clinicians must be able to formulate an appropriate treatment plan while minimizing the damage caused by the disease process on

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case-to-case basis. In this regard, the present review would serve to guide the clinicians in taking a prompt decision on how to proceed with the management of patients with BRONJ.

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Legend Table

Table 1: Clinical staging and recommended treatment of BRONJ as proposed by AAOMS (2009)

Stage	Bone Pathology	Symptoms	Management
At risk category	No apparent necrotic bone	None	Preventive measures
Stage 0	No clinical evidence	Present but non-specific	Antibacterial mouth rinses, Palliative care
Stage 1	Exposed and necrotic	Asymptomatic without any evidence of infection	Antibacterial mouth rinses + systemic antibiotics
Stage 2	Exposed and necrotic	Pain, erythema, with or without pus discharge	Antibacterial mouth rinses + systemic antibiotics + surgical debridement+ palliative care
Stage 3	Exposed and necrotic bone either extending beyond the region of alveolar bone, (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the	• Pain and infection • Extra-oral fistula • Oral antral/oral nasal communication	Resection with 'add-on' therapies+ systemic antibiotics+ and palliative care

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	maxilla) resulting in pathological fracture		

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