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Original Research

Different treatment modalities of BRONJ: Our clinical experience

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***ABSTRACT*:**
The mechanism of action of bisphosphonates (BPs) is not yet well understood, but it essentially involves a powerful inhibition of bone resorption as a result of the reduction of osteoclast activity; as far as nitrogen-containing BPs are concerned they are also thought to have antiangiogenic effects. Osteonecrosis of the jaws has recently emerged as a significant complication in a subset of patients receiving these drugs. Based on a growing number of case reports and institutional reviews, bisphosphonate therapy may cause exposed and necrotic bone that is isolated to the jaw. Treatment with bisphosphonate drugs is associated with several complications including renal and gastrointestinal side effects, particularly oesophageal ulceration, but the most serious is that of osteonecrosis of the jaw (bisphosphonate-related osteonecrosis of the jaw – BRONJ).

Key words: Bisphosphonates, Necrosis, Jaws

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INTRODUCTION

Widespread bisphosphonate (BP) use to treat various medical conditions led to increased recognition of their possible association with osteonecrosis (ON) of the jaw. BPs are synthetic pyrophosphate analogs used to treat hypercalcemia secondary to malignancy, osteoporosis, multiple myeloma, Paget disease, osteosclerosis, fibrous dysplasia, and other bone diseases in which bone resorption is involved. Infrequent side effects with BP use include pyrexia, renal function impairment, hypocalcemia, and recently recognized avascular ON of the jaw. The American Society of Bone and Mineral Research defined BP-related jaw ON as current or previous treatment with BPs that leads to exposed bone in the maxillofacial region that does not heal within 8 weeks of identification by a healthcare provider, and the patient has no history of radiation therapy in the craniofacial region. Eight weeks is considered because most surgical and infectious sites heal in this time frame even if complications such as postsurgical infection, chemotherapy, or systemic diseases are present.[1-3]

BISPHOSPHONATES

Biochemical interactions between the bone microenvironment and cancer cells create a vicious cycle that promotes bone destruction and tumor growth. In patients with advanced malignancy, the primary tumor invades the bone and causes skeletal metastases. The metastasis disrupts the normal bone homeostasis by expressing growth factors and cytokines that accelerate osteoclast activity. Bone metabolism is excessive and leads to skeletal morbidity with bone pain, hypercalcemia, pathologic fractures and spinal cord compression.[4-6]

Regulation of the normal bone homeostasis occurs via the RANK/RANKL/OPG pathway, in which the osteoblast lineage regulates the differentiation and activity of osteoclasts. This pathway involves three major components: receptor activator of nuclear factor B

(RANK), which is expressed on the surface of osteoclast precursor cells; RANK ligand (RANKL), a polypeptide found on the surface of osteoblast cells and proteolytically released as a soluble form; and osteoprotegrin (OPG), which is a receptor produced by osteoblasts. Because differentiation and activation of osteoclast precursor cells into mature osteoclasts requires binding of RANKL to RANK, excessive bone resorption is prevented by OPG which binds to RANKL and avoids the interaction between RANKL and RANK. This interaction is lost when cancer cells invade the bone microenvironment and induce excessive osteolysis, due to the increase of parathyroid hormone-related protein, which stimulates RANKL production by osteoblasts, and to the decrease of osteoblastic OPG.[4- 6]

PATHOGENESIS

Despite the possibly linking theories, the pathogenesis of BRONJ has not been entirely understood. One of the underlying factors is the suppression of natural remodeling process due to the inhibition of osteoclasts. Remodeling is vital for bone healing and the suppression by bisphosphonates diminishes the healing capacity of the bone. It is not obvious whether bisphosphonates are found in the tissues at a high enough concentration to generate toxic effect on soft tissue in vivo, during normal oral administration. However, in vitro they produce direct toxic effect on the soft tissues of the oral cavity, which can also play a role in the development of BRONJ. Due to the antiangiogenic features of bisphosphonates, there may be a quantity of decline in the vascularity of bone. However, the histological studies have not endorsed this suggestion, thus reduction in vascularity seems not likely to have a significant role in the initiation of BRONJ. The particular occurrence of osteonecrosis due to bisphosphonates in the jaws area is in part related to the high turnover of alveolar bone as well as the exposure of jaw to the outside environment through the teeth and periodontal ligament.[7- 9]

TREATMENT

To date, treatment option for patients with BRONJ is limited and predominantly palliative, aiming at relieving the main signs and symptoms. Marx et al. recommend that treatment should eliminate and control pain, as well as preventing progression of bone exposure through antibiotics therapy and mouthwash with 0.12% chlorhexidine. They also state that conservative surgical treatments are preferential, aiming at nonexposure of necrotic bone boundaries. AAOMS in 2009 recommended the removal of well-defined bone sequestrations, as well as the removal and/or relining of bone necrosis areas which are a constant source of irritation to soft tissues.[10]

Montebugnoli et al also recommended the management of osteonecrosis with nonsurgical protocol. These authors conducted a study dividing patients into two groups, one treated with surgery and the other treated with antibiotics. Data analysis showed there was no statistically significant difference between outcomes for the two groups.[11]

Curi et al reported on three clinical cases in which sequestra removal was performed and autologous platelet-rich plasma was topically applied onto the remaining defect. After six-month follow-up, complete repair of surgical site was seen, thus showing promising results.[12]

Discontinuation of oral BPs in BRONJ patients has been associated with gradual improvement of clinical disease. Discontinuation for 6–12 months may result in sequestration with spontaneous resolution after surgical debridement. Whenever systemic conditions permit, changing or stopping oral bisphosphonate treatment must be a result of an agreement between the professionals involved and the patient.[13]

Previous studies have shown that the cumulative hazard of developing BRONJ is significantly greater with zoledronate treatment than with pamidronate or pamidronate plus zoledronate. It has been hypothesized that inhibition of angiogenesis leads to jaw necrosis. Because maxillary and mandibular alveolar bone has a quicker bone turnover rate than that of other bones, n-BIS might be highly concentrated in the jaws. Coupled with the antiangiogenic properties, this anatomic concentration of n-BIS would make the alveolar bone more susceptible to BRONJ.[14- 16]

Patients amenable to conservative management would be those considered to be at risk and/or individuals without symptoms. Conservative management includes the reinforcement of oral hygiene, periodic dental checks, oral rinses with chlorhexidine, and antibiotic treatment. In this regard, the most widely used antibiotics are amoxicillin with or without clavulanic acid (500 mg/1 g) clindamycin (300 mg), azithromycin (500 mg) and in some cases the combination of metronidazole with betalactams. Ozone therapy stimulates cell proliferation and soft tissue healing, and reduces pain, with promising results in phase I/II clinical trials. Hyperbaric oxygen (HBO) has sometimes been used in application to BRONJ, with controversial results. Low-intensity laser therapy (LILT) has been shown to be an innovating and effective treatment in medicine, with effects that include the lessening of pain, improved wound healing, and the facilitation of nerve regeneration. Pentoxifylline and α-tocopherol have been suggested to assist antimicrobial therapy in the early stages of BRONJ, since these substances have been found to reduce the bone exposure area and symptoms in 74% of the cases. In those patients in which previous treatment has failed, or in very advanced cases of BRONJ, resective or extensive (segmental) surgery is indicated with the purpose of eliminating all the necrotic tissue, leaving only healthy bone. However, resective surgery has generated controversy, since in many cases it is difficult to eliminate all the necrotic bone and guarantee the obtainment of healthy bone margins.[17- 26]

Healing following BRONJ treatment is defined based on clinical evidence of stable oral mucosal coverage—a

criterion adopted by the vast majority of surgical studies. However, oral mucosal coverage does not necessarily reflect the absence of underlying necrotic bone. Despite several studies that have suggested that a clinical follow-up period of 6 months is sufficient for confirming a cure, there is increasing evidence that some BRONJ may recur 1 year or more after the completion of surgery. In most cases, it is generally recommended to completely close the surgical wound following the removal of a lesion, and a wound is often assessed as having healed if there is no dehiscence. However, as previously mentioned, some recurrence are observed more than 1 year following BRONJ treatment. Such findings may be due to the presence of remaining necrotic bone underneath the mucosa, despite the appearance of having achieved healing at the soft tissue level after complete closure.[27- 29]

In our experience conservative non-surgical management is a valid approach to BRONJ considering the poor health of BRONJ affected people. It is very important that preventive measures are always taken in order to subvert the risk of developing this severe complication. These include careful dental examination and preventive extractions of candidate teeth with enough time allowed for healing in advance of the start of BPs treatment. Moreover, all patients taking BPs have to be informed of the benefits and risks of treatment and encouraged to maintain good oral hygiene (including regular dental visits).

CONCLUSION

Bisphosphonates are one of the most prescribed drugs all around the world. Although it is a rare condition, potential risk of BRONJ due to oral bisphosphonates should not be neglected. Of the patients on oral bisphosphonates, those with appropriate dental care do not require a dental examination prior to the initiation of treatment. However, patients who are not receiving regular dental care or with concomitant risk factors such as cancer, corticosteroids, chemotherapy, and poor oral hygiene should undergo a broad oral examination by a dentist either prior to or following the initiation of bisphosphonates. Data on the use of antibiotic therapy together with surgical debridement and local placement collagen-gentamycin sponge indicate positive results regarding the surgical treatment of BRONJ.

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