

Review Article

Bisphosphonate - Associated / Related Osteonecrosis of the Jaw (Bronj)- Current Diagnosis, Pathogenesis and Treatment

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Abstract

The introduction of oral and parenteral bisphosphonates (BPs) into routine clinical practice has reduced the number of cases of pathological fractures, bone metastasis, and has significantly reduced the risk of hypercalcemia in oncologic patients. It has been shown in vitro that BPs promotes proliferation and differentiation of human osteoblast-like cells and inhibits osteoclast. Diagnosis of Bisphosphonate related osteonecrosis of the jaw (BRONJ) should be based mainly on radiographic and clinical findings. Currently, the treatment is done based on staging and guidelines by American Association of Oral and Maxillofacial Surgeons.

Key Words: Bisphosphonates, Osteonecrosis, Jaw, BRONJ

Introduction

Bisphosphonates (BPs) are drugs that prevent resorption of bone by acting specifically on osteoclasts, enabling to maintain bone density and thereby strength of the bone.¹ Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as a non-healing wound with exposed bone, persisting for more than 8 weeks in a patient receiving bisphosphonates and with no history of local radiation therapy.² Bisphosphonates are being used in various clinical settings, including prevention and treatment of osteoporosis, hypercalcemia, Paget's disease of the bone, osteolysis associated with bone metastases of various malignant tumors and multiple myeloma.³

BPs has been quickly applied to treat bone dysplasia, prevent bone loss in osteoporosis, various metabolic diseases of bone, and improve the stability of endoprosthesis.⁴ Bisphosphonates act both on osteoclast and osteoblast, promoting proliferation and differentiation of osteoblast and inhibit osteoclast activity.⁵ BPs are synthetic analogs with a P-C-P bond which is used as a bone - specific radionuclide in technetium 99m methylene diphosphonate (Tc 99mMDP) scan of bone. Bisphosphonates in general are resistant to breakdown by enzymatic hydrolysis, which enables their accumulation into the bone matrix and their long half-life.⁶

Some of the adverse effects of BPs were known initially prior to its clinical usage such as increased body temperature, atrial fibrillation, gastrointestinal symptoms, and its harmful effects on the kidneys.⁷ For patients on bisphosphonates, surgical procedures which expose the bone increase their risk of developing

BRONJ and thereby leading to various complications post treatment.^{8,9} Bisphosphonates offers significant clinical benefits in conditions where an imbalance between bone formation and bone resorption of an underlying disease exists; however, recently recognized association of oral and parenteral bisphosphonates use with pathologic conditions, including lower bone turnover rate with increased frequency of pathologic fractures, osteonecrosis of the jaw (ONJ), and an increased rate of atrial fibrillation. These have brought increased scrutiny to the current broad use of bisphosphonate therapy in treatment of various diseases.⁷

Clinical Signs and Symptoms

Clinically, BRONJ presents itself as exposed and often dead alveolar bone that becomes visible following any invasive procedure such as extractions or periodontal treatment. Signs and symptoms that may present before the clinically detectable osteonecrosis includes tooth mobility, mucosal swelling, pain, erythema and ulceration in oral cavity. Patients may also present with difficulty with speaking and eating, trismus, bad breath and recurrent dental abscess. The incidence of ONJ in bone malignancies treated with high dose intravenous bisphosphonates is about 1-12%.¹⁰ In treatment of osteoporosis with bisphosphonate the incidence of BRONJ is similar to normal individuals. Epidemiological studies indicate an average estimate of less than 1 case per 100 000 person / years of exposure to oral bisphosphonates therapy.⁹

An association between IV bisphosphonate use and BRONJ may be deduced based on the following observations: 1) a positive correlation between

bisphosphonate efficacy and risk for developing BRONJ; 2) a negative correlation between bisphosphonate potency and duration of bisphosphonate exposure of patient prior to developing BRONJ; and 3) a positive correlation between duration of bisphosphonate exposure and developing of clinically detectable BRONJ.¹¹

Clinical Staging

American Association of Oral and Maxillofacial Surgeons has given a clinical staging for BRONJ¹² which is as follows,

Stage 0: Patients with no clinical evidence of necrotic bone, but present with non-specific symptoms or clinical and radiographic findings

Stage 1: Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection.

Stage 2: Exposed and necrotic bone in patients with pain and clinical evidence of infection.

Stage 3: Exposed and necrotic bone in patients with pain, infection, and one or more of the following:

- Exposed necrotic bone that extends beyond the alveolar bone, i.e., inferior border of mandible and ramus of the mandible, maxillary sinus and zygomatic process of maxilla
- Pathologic bone fracture
- Extra-oral fistula
- Oral antral/oral nasal communication
- Osteolysis that extends to the inferior border of the mandible or sinus floor within maxilla

Etiopathogenesis

Etiology:

The etiology of ONJ remains unclear and uncertain. Initially, when the condition was called bisphosphonate related osteonecrosis of the jaw (BRONJ), its similarities with radiation-induced osteonecrosis led to the assumption that the condition started with sterile necrosis of the jaw bone which led to the term osteonecrosis, but later it was found that this was not sterile from start.

Pathogenesis:

There is no proven pathogenesis of BRONJ but various authors have proposed hypothesis for its pathogenesis of which Woo et al¹³ and Reid et al¹⁴ and are quite widely accepted.

Hypothesis 1: One of the proposed hypotheses for osteonecrosis by Woo et al says that chronic usage of bisphosphonates causes a continued inhibition of osteoclast and decreases the bone vasculature which in turn affects the remodeling and physiology of bone causing an irreversible block of mevalonate pathway, affecting bone turnover causing osteonecrosis of jaw.¹³

Hypothesis 2: Reid and Rolland proposed an alternate hypothesis for BRONJ, which says that chronic use of bisphosphonates causes its accumulation in bone. This accumulation with time reaches toxic levels affecting the oral epithelial remodeling. Once this occurs even a minor trauma can lead to BRONJ.¹⁴

Histopathology Of BRONJ

Diagnosis of BRONJ should be based mainly on clinical and radiographic findings. Tissue biopsy is often not necessary and should be done only if metastatic spread of the disease is suspected. Histological examination of the specimen shows, areas of partially or completely necrotic alveolar bone, debris and fibrinous exudates along with an inflammatory infiltrate of histiocytes, neutrophils, eosinophils and plasma cells. The non-vital alveolar bone exhibits loss of pattern of osteocytes within the lacunae, peripheral bone resorption and various bacterial colonization. Sequestrum and abscess formation are commonly noted. Specimens of superficial sequestrum often show necrotic bone surrounded by large number of bacterial colonies.¹⁵

The histological features are quite similar to that observed in chronic Osteomyelitis. However, it remains doubtful whether the inflammatory process occurs due to a super infection of necrotic and dead bone or rather occurs as a secondary phenomenon of microbial invasion of metabolically slow and poorly vascularized bone. The fact that bone tissue around the area of lesion shows some degree of viability supports the hypothesis that bone damage is initiated by an injury or an infection and is aggravated by the reduced remodeling capacity of bone as a result of bisphosphonates therapy ultimately compromising the reparative process of bone.^{16,17}

Prevention Of BRONJ

Until a better understanding of bisphosphonates role in the pathobiology of BRONJ develops, it is important that preventive measures be taken to reduce the risk of developing BRONJ. This should include thorough clinical examination and extraction of all infected teeth or teeth with poor or hopeless prognosis with adequate time allowed for healing of bone to occur prior to starting bisphosphonate therapy. Following radiation it is recommended that bisphosphonate treatment be delayed until there is sufficient bone healing. Of supreme importance is to adopt preventive measures such as control of dental caries and periodontal disease, usage of soft liners on dentures and avoiding placement of dental implants. This level of preventive care should be continued by the patients to reduce their risk of developing BRONJ.^{18,19}

Treatment

Various treatment modalities have been reported in literature, including conservative management, surgical management, hyperbaric oxygen therapy, and ozone gas therapy and laser treatment. The current treatment guidelines are mainly based on expert opinions, because of the paucity of prospective randomized clinical trials. The American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed a staging system to help provide better and case specific treatment for any given patient.¹² (Table-1)

Table-1: Treatment protocol suggested by American Association of Oral and Maxillofacial Surgeons ¹²

Stage	Treatment
STAGE 0	Provide symptomatic treatment, and conservatively manage other local factors, such as caries and periodontal disease. No surgical treatment is indicated
STAGE 1	These patients benefit from the use of oral antimicrobial rinses, such as chlorhexidine 0.12%. No surgical treatment is indicated.
STAGE 2	These patients benefit from the use of oral antimicrobial rinses in combination with antibiotic therapy. No surgical treatment is indicated.
STAGE 3	These patients benefit from debridement, including resection, in combination with antibiotic therapy, which may offer long-term palliation with resolution of acute infection and pain.

Conclusion

Oncology patients benefit significantly from bisphosphonate therapy, as the therapy controls bone pain and reduces the occurrence of pathologic bone fractures. Bisphosphonate surely cause a lot of adverse effects but their clinical effects surpass the negative complications and hence even though they may cause dreadful BRONJ they are extremely useful for patients. Proper hygiene and systemic health maintenance can significantly reduce incidence of BRONJ.

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