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Use of Bisphosphonates and The Effect of Osteonecrosis of The Jaw – Review

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ABSTRACT

Bisphosphonates are highly efficient antiresorptive drugs used to treat diseases with increased osteoclast activity such as cancer-related conditions, osteoporosis, multiple myeloma, Paget disease, osteosclerosis, and fibrous dysplasia. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as a current or previous treatment with BPs that leads to an exposed bone or bone that can be probe through a fistula in the maxillofacial region that does not heal within eight weeks.

1. ETIOLOGY

Bisphosphonates inhibit bone resorption by causing osteoclast cell apoptosis, impairing the osteoclast's resorptive capacity, and preventing osteoclast formation. They have a high affinity for bone minerals and accumulate mainly in the sites of osteoclast activity.[1] Without resorption and new bone formation, old bone survives beyond its lifespan, and its capillary network is not maintained, leading to avascular necrosis of the jaw. Also, high potency biphosphonates can lead to necrosis by the toxicity of soft tissue and bone cells, further complicated by infection.[2] Due to altered wound healing, delayed epithelial closure of a mucosal opening in the mouth leads to chronic infection and the necrosis of bone. Osteonecrosis develops in the jaw because this bone has a higher remodeling rate than other bones, making it more prone to the effect of bisphosphonates

Risk Factors

Several factors increase the risk of developing bisphosphonates-related osteonecrosis of the jaw:

1) Invasive oral procedures such as tooth extraction, periodontal surgery, and oral implant placement, and the use of dentures increase the rate of bone turnover and the risk of osteonecrosis.

2) Comorbidities like cancer, chemotherapy, low hemoglobin levels, diabetes mellitus, renal dialysis, hypertension, hyperlipidemia, and hypercholesterolemia

3) Concomitant medications: corticosteroids and H2 blocking drugs, which increase BP absorption. Antiangiogenic agents, particularly sunitinib and bevacizumab. Erythropoietin and cyclophosphamide therapy.

4) Infection: it is still unclear if osteonecrosis precedes or follows the infection. However, polymorphonuclear aggregates and bacterial microfilm in the surrounding tissue have been associated with bone resorption and necrosis.

BPs inhibit the proliferation and viability of oral keratinocytes, damaging the oral mucosa integrity and increasing the risk of infection. Also, BPs impair the immune response to infection by activating gamma, delta T-cells stimulating the production of pro-inflammatory cytokines and later depletion of T cells.

5) Genetic predisposition: polymorphism in farnesyl pyrophosphate synthase or CYP2C8 coding for a cytochrome P450 enzyme predisposes some individuals to bisphosphonate-associated osteonecrosis of the jaw in multiple myeloma.

6) Other risk factors include increasing age, alcohol, and tobacco use.

Complications of BRONJ include tissue ulceration, intra-and extraoral sinus tracts, and fistula.[3] Chronic maxillary sinusitis in patients with maxillary bone involvement and fracture in edentulous patients with oral implants have also been reported.

Signs and Symptoms

1. None/asymptomatic
2. Pain
3. Soft tissues infection with inflammation, ulceration, and suppuration
4. Formation of intra-and extraoral sinus tracts and fistulas
5. Paresthesia or anesthesia of an associated nerve
6. Fracture
7. Chronic maxillary sinusitis
8. A radiographic appearance from no alterations to varying radiolucencies and radiopacities

2. EVALATION

Blood Test

It measures the C-terminal telopeptide (CTX) value, which depicts the level of octapeptide fragment released due to osteoclastic bone resorption from type I bone collagen.[4] Its levels are related to the number of osteonecrotic lesions, stage of disease, and bone turnover index. A lower value represents a high-risk patient with suppressed bone turnover and reduced healing capacity. C-terminal telopeptide less than 100 pg/ml equals high risk, 100 to 150 pg/ml equals moderate risk, and greater than 150 pg/ml equals minimal or no risk.

Radiographic Appearance

Radiographically, BRONJ can range from no alterations to varying radiolucencies or radio-opacities. Osteolytic lesions may appear less or more radiodense, providing a similar radiographic appearance as metastatic bone. Altered bone morphology, periosteal bone formation, increased bone density, or sequestration may be radiographic findings of BRONJ. Early radiographic signs along alveolar bone may include widened periodontal ligament space and sclerosis of lamina dura.

Imaging Modalities and Diagnostic Tests

Due to the nonspecific radiographic features of the condition, imaging provides a good evaluation of the area involved and can assist in identifying the extent of bone and soft tissue disease but does not provide any definitive differentiation of osteonecrosis of the jaw from other conditions.[5]

Conventional radiographs

Intraoral and panoramic radiographs are easy to acquire, inexpensive, deliver low radiation, and provide a good view. They are helpful to assess early features: thickening of lamina dura, increased trabecular density, incomplete healing of extraction socket, widening of periodontal ligament space, sinus floor cortication, periosteal bone, and sequestrum formation. Poor quality images do not clearly demarcate between necrotic and healthy bone. Disease at early stages can be frequently missed. Despite limitations, they form the first line of routine radiological investigation.[6]

Cone beam CT scan

Cone beam CT scan provides tridimensional imaging of the involved cancellous and cortical bone and identifies osteosclerotic and osteolytic regions. It can also evaluate sequestrum, periosteal bone reaction, and the integrity of the vital adjacent structures [7], potential fistula tract, cortical erosion, and incomplete extraction socket healing.

The early stage of osteonecrosis may not be detected, but cortical and trabecular bone changes at the symptomatic site can aid in diagnosis. CBCT has similar findings of the osteonecrotic areas as the CT scan but imparts lower radiation and has higher spatial resolution with better image quality, particularly for the cancellous bone in a small field of view. The major limitation is poor soft tissue details due to low contrast resolution.

MRI

MRI currently may be the method of choice to detect the early bone marrow and soft tissue changes surrounding the

osteonecrotic area. Osseous change evaluation by MRI is similar to CT imaging. One consistent MRI findings are the decreased bone marrow signal intensity on T-1 weighted images resulting from progressive cell death and host response through repair, i.e., edema.[8] Irregular gadolinium enhancement around osteolytic lesions is observed. An MRI shows non-enhancement in regions of ischemia, especially in T-1 weighted sequences, low signal intensity in areas of fibrosis and sclerosis on T-1 and T-2 weighted images, and increased signal intensity along the unexposed diseased bone. However, MRI may not demonstrate the full extent of bony changes and may give a false-positive diagnosis.

Nuclear Imaging with Bone Scintigraphy

Technetium-99 radioisotope scintigraphy has a high sensitivity for diagnosing early disease and ischemic osteonecrosis. Its sensitivity depends on the stage of osteonecrotic lesion and the change in vascularity. It shows increased radionuclide uptake in surrounding areas with increased perfusion and blood pool, locating osteonecrotic regions more precisely.

The main drawbacks include significant radiation exposure, lengthy procedure, and low resolution, which sometimes make it challenging to differentiate between inflammatory and metastatic processes and heal osteolytic lesions and progressing osteoblastic lesions.

Combining CBCT with scintigraphy for diagnosing osteomyelitis [8] or using contrast agents with MRI, sequential imaging, and manipulating image planes can all be helpful measures to diagnose early or preclinical stages of BRONJ.

Treatment / Management

Treatment depends on age, gender, disease stage, lesion size, comorbidities, and medication. Still, since their influence on disease course and treatment response is unknown, clinical judgment guides the treatment approach. Other important factors are prognosis, life quality expectancy, and the patient's ability to cope with the disease.

No evidence-based guidelines for the treatment of BRONJ are currently available, but the treatment goal is to alleviate pain, control infection, and stabilize the progression of exposed bone.

Conservative Therapy

The mainstay of care is conservative therapy, and this may provide long-term symptomatic relief.

1. Pain control and optimal oral hygiene, including diligent home care and regular dental visits.
2. Managing infection and active dental disease: use of 0.12% chlorhexidine digluconate oral antimicrobial rinses and systemic antibiotic therapy.[9] Penicillin VK, 500 mg, four times daily is the antibiotic of choice. This formulation of penicillin is non-toxic and can be used long-term without superinfection and development of candidiasis. If long-term antibiotic usage is a concern, then it can be taken only during episodes of pain. If the patient is allergic to penicillin, then levofloxacin, 500 mg, once daily, is the best alternative. Other alternatives include doxycycline, 100 mg daily, or azithromycin, 250 mg daily. However, levofloxacin and azithromycin should be used for only 21 days or less due to their potential to raise liver enzymes. If this antibiotic protocol is ineffective, adding 500 mg of metronidazole three times daily for ten days is recommended.
3. Teriparatide improves osseous wound healing in the oral cavity.[10] However, it is not recommended for patients at low risk of osteonecrosis of the jaw or fracture, but adding it to the treatment regimen of the osteoporotic patient with established osteonecrosis may benefit them.[11] The same approach is not recommended for a cancer patient or those who have received skeletal radiation or have active bone metastasis. These patients have a risk of development or advancement of bone malignancies.
4. Reduce the contact of the oral prosthesis with the exposed bone.
5. Repeat the C-terminal telopeptide test (CTX) after six months of drug holiday. Some cases resolve with CTX value rising above 150 pg/ml. Many show clinical and radiographic signs of improvement as separation of necrotic bone from healthy bone occurs, followed by sequestration and debridement. Most of the oral BRONJ cases are resolved by CTX guided protocol. Regular follow-ups must be done to keep the CTX value above 150 pg/ml using incremental drug schedules and alternative drugs.

Surgical Therapy

Lack of symptomatic or radiographic improvement with various treatment modalities indicates permanent bone defect and need surgical intervention.

1. The osteotomy of the affected area needs to be performed with resection margins extending into the adjacent healthy bone. Soft tissues should be closed with a tension-free closure and no underlying sharp edges that could lead to a mucosal breakdown.[12]
2. Microvascular composite tissue grafting and reconstruction procedures should be considered in patients with pathological fractures, disease extending to the sinus or inferior border of the mandible, or if osteotomy leads to

discontinuity defect.

Experimental Therapy

The various treatment approaches include the use of hyperbaric oxygen , bone marrow stem cell intralesional transplantation [13], local application of platelet-derived growth factor, low-level laser therapy, or using them in combination with conservative or surgical debridement, but their effect on the treatment outcome needs further substantiation.

The most recent recommendations advocate a non-surgical treatment approach due to impaired wound healing. Still, few studies included radical resection to viable bone and hermetic wound closure, with soft tissue being the only curative approach.[14] Combining various approaches like marginal resection and platelet-derived growth factors as been advocated by many studies.

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