Bisphosphonates induced Osteonecrosis of the Jaw: A review

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Abstract - Bisphosphonate therapy is used extensively to treat osteoporosis and osteolytic bone lesions. Recently, a special form of osteonecrosis limited to the maxillofacial skeleton has been discovered especially with the use of IV nitrogen containing Bisphosphonates. Bisphosphonates accumulate almost exclusively in maxillofacial skeleton due to high bone turnover remodeling to maintain mechanical competence. The pathogenesis, and why it commonly appears in maxillofacial skeletons, and the fixed treatment strategies remains unknown. The aim of this study was to improve the clinician understanding of Bisphosphonates associated osteonecrosis of the jaws by reviewing the past 10 year literature.

Key words - *Bisphosphonates, osteonecrosis of the jaw*

1 INTRODUCTION

Bisphosphonates (BPs) are stable analogs of pyrophosphate, which are naturally occurring modulators of bone metabolism and have been synthesized and used since the 19th century but their in-vitro ability to inhibit the precipitation of calcium phosphate was applied clinically in 1960s. They are poorly absorbed by the gastrointestinal tract (about 10%) and excreted largely unchanged by the kidneys but if given IV, about half of the drugs goes to the bone.[1,2] BPs are commonly used to treat certain resorptive bone diseases such as osteoporosis, Paget's disease and hypercalcemia associated with certain malignancies such as multiple myeloma and bone metastasis from the breast or prostate.[3,4] Their principal action is to inhibit resorption of bone by inhibiting osteoclast activity, which results in an increase in the mineral density of bone and a reduction in serum calcium,[2] although other actions such as inhibition of angiogenesis have also been reported.[5]

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BPs has unique pharmacokinetic properties, like long retention time in bone; it is possible that beneficial effects on fracture risk may persist for some time after treatment is stopped.[6] BPs has a high affinity for exposed hydroxyapatite within bone mineral and within bone is metabolically inactive. As the process of metabolic bone resorption progresses, previously bound BPs is released and exerts their clinical effect.[2]

There are two classes of BPs which have different mechanism of action on osteoclasts based on presence or absence of a nitrogen side chain on the pyrophosphate group. Non-nitrogen containing BPs (Tiludronate, Clodronate and Etidronate) is taken up by the osteoclasts and antagonized the cellular energy pathways due to intracellular liberation of methylene that contains toxic analogs of ATP, which probably inhibit ATP-utilizing enzymes and induce osteoclast apoptosis. Nitrogen containing BPs (Zolendronate, Pamidronate, Alendronate, Ibandronate and Risedronate) has a more complex pathway of action where they inhibit the Mevalonate pathway by inhibition of farnesyl pyrophosphate synthetase leads to prenylation of small GTPase signaling proteins that are essential for osteoclast activity and survival. According to previous literature, Zoledronate has also been shown to inhibit human endothelial cell to proliferate and to modulate endothelial cell adhesion and migration.[1, 2, 3, 7]

Therefore a possible association was seen between BPs and two rare but serious conditions, namely atypical femoral fracture and osteonecrosis of the jaw (ONJ).[6]

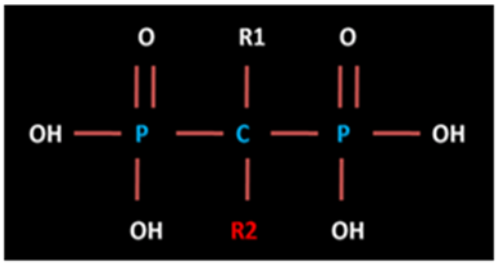
Current working definition of BRONJ has been adopted by the AAOMS "Patients may be considered to have BRONJ if all of the following three characteristics are present: 1) Current or previous treatment with a Bisphosphonates, 2) Exposed bone in the maxillofacial region that has persisted for more than eight weeks; and 3) No history of radiation therapy to the jaws. According to NSW Health Guideline, an additional character was added in AAOMS working definition of BRONJ; there is no evidence of cancer at the site.[4, 8] Incidence of BRONJ was 0.8% to 12%[4,8] in IV BPs and 0.01% to 0.04%[4] in oral BPs administration.

2 ETIOLOGY AND PATHOGENESIS OF BPS INDUCED ONJ

Chemical structure of Bisphosphonate **(Figure-1)**, have two important entity P-C-P backbone and R2 side chain that shows a strong affinity for bone mineral and provides potent inhibition of bone turnover both in vivo and in vitro and therapeutic potency of the BPs respectively. BPs inhibits bone resorption by inhibiting osteoclastic activity. Nitrogen containing BPs had poorly absorbed by GIT because of its more complex metabolism as compare to non-nitrogen containing BPs at R2 side chain. Due to this region nitrogen containing BPs are commonly prepared for IV administration.[2, 4, 8]

FIGURE -1

CHEMICAL STRUCTURE OF BISPHOSPHONATES



PCP Group: Essential for biological activities-binding hydroxy apatite, **R2 Side Chain**: Determines Potency.

Bone remodeling is a physiologically coordinated process involving bone formation by osteoblasts and bone resorption by osteoclasts. Imbalance between these two entities may lead to skeletal abnormalities characterized by increases or decreases in bone density.[9] In contrast to other skeleton, jaw bones (alveolar process and Periodontium) have relatively high vascularity, bone turnover and remodeling because of continuous mechanical stress.[3] Such bone repair and remodeling is greatly enhances by infection and/or trauma.[10] Non-Nitrogen containing BPs are metabolized intracellular into methylene that contains toxic analogs of ATP, which probably inhibit ATP-utilizing enzymes and induced osteoclast death whereas nitrogen containing BPs inhibit the enzyme Farnesyl pyrophosphate synthase leads to prenylation of small GTPase signaling proteins that are essential for osteoclast activity and survival.[3, 11] Although the exact Pathophysiology of BPs induced osteonecrosis of the jaw has not be completely illuminated but according to previous literature, BPs are potent inhibitors of osteoclastic activity, angiogenesis, human endothelial cell to proliferate and to modulate endothelial cell adhesion and migration. [2, 8, 12, 13] Thus the net result is that the jaw bone is unable to meet the peak demand for bone repair and remodeling that may finally lead to BPs induced ONJ.

3 CLINICAL PRESENTATION AND DIAGNOSIS OF BPS INDUCED ONJ

According to ASBMR, confirmed case of ONJ was defined as "An area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a BPs, and no history of radiotherapy to the craniofacial region".[14, 15] In January 2009 (AAOMS) Proposed a similar working definition for BPs associated ONJ but in 2010 (NSW Health Guideline), an additional character was added in AAOMS working definition of BPs associated ONJ; there is no evidence of cancer at the site. [4, 8]

The clinical appearance of BPs associated ONJ is identical to the appearance of Osteoradionecrosis in patients who develop it after undergoing craniofacial irradiation.[16] Severe cases of BPs associated ONJ can causes intense pain, extensive sequestration of bone and cutaneous draining sinus tracts.[17, 18] According to Lam DK et al,[9] Common orofacial findings associated with BPs associated ONJ are Poor wound healing, Spontaneous or postsurgical soft-tissue breakdown leading to intraoral or extraoral bone exposure, Bone necrosis and Osteomyelitis.

Radiographic appearance of BPs associated ONJ, previous literature provide some valuable information with different imaging technique like **Periapical radiograph / CBCT** (Osteosclerosis involving the cortical bone, alveolar margin, lamina dura, mixed sclerotic and lytic bone destruction, and sequestra. But thickening of cortical plate was the only radiological findings of CBCT), [19] **CT images** (Sclerotic changes, Osteolytic changes, Periosteal bone proliferation, Sequestration and Inferior alveolar canal involvement)[20], **Contrast enhanced MRI images** (Intensity changes of the cortical and sub cortical bone structures, Contrast enhancement in necrotic bone area, Soft tissue involvement and Cervical lymphadenopathy) [20] and **$^{99}Tc^{m}$ – MPD** three phase bone scans was used to detect subclinical osteonecrosis.[21]

According to previous literature, some important serological, histopathological and immunohistochemistry findings are obtained in cases of BPs associated ONJ. Like decreased VEGF level,[5] morning fasting serum C-terminal telopertide (CTX) value [less than 100 pg/ml] representing high risk of BPs associated ONJ),[9,22,23] Histopathology examination (may reveal small non vital bone fragments with bacterial colonies and absence of inflammatory cells)[9] and immunohistochemistry reveals (increased expression of hDB-1,-2,-3, reduced expression of TGFβ1 and increased Galectin-3 expression) in BPs associated ONJ.[24,25]

According to recent position paper by AAOMS and NSW Health Guideline, risk factors for the development of BPs associated ONJ can be grouped as drug-related, local, demographic and systematic, Genetic and preventive are summarized **Table-1**.

TABLE 1

RISK FACTORS OF BPS ASSOCIATED ONJ

Risk factors	Literature of review
Drug related	
1. Potency of BPs	More potent BPs have more tendency to developed ONJ
2. Route of drug administration	IV route of administration result in greater drug exposure than the oral route, therefore more tendency to developed ONJ if given IV
3. Duration of therapy	Longer duration appears to be associated with increased risk
Local	
1. Dentoalveolar surgery	Patients receiving IV BPs and having dento-alveolar surgery are seven times more likely to develops ONJ than patients who are not having dentoalveolar surgery
2. Anatomic location	BPs associated ONJ is more common in the mandible than in the maxilla (2:1) and more common in areas with thin mucosa overlaying bony prominences (Tori, Bony exostoses and mylohyoid ridge)
3. Concomitant oral diseases	Cancer patients exposed to IV BPs with history of inflammatory (possibly infective) dental diseases are at a seven-fold increased risk for developing ONJ
Demographic/systemic	
1. Age	With each passing decade – there is a 9% increased risk of ONJ in multiple myeloma patients treated with IV BPs but sex was not statically associated with ONJ
2. Cancer type	Multiple myeloma >> breast cancer > other cancer and Osteopenia/Osteoporosis concurrent with cancer are more prone to developed ONJ
3. Concomitant risk factors	Renal dialysis, low hemoglobin, Obesity, Diabetes, Chemotherapeutic agents (Cyclophosphamide, erythropoietin and steroids), Tobacco users and poor oral hygiene are risk factors but no increased risk associated with alcohol exposure
Genetic	Genetic perturbations (single nucleotide polymorphisms), in the cytochrome P450-2C gene (CYP2C8) gene were associated with an increased risk for ONJ among multiple myeloma patients treated with IV BPs.
Preventive	Dental evaluations and receive necessary treatment prior to initiating IV BPs therapy. Manipulation of IV BPs dosing may be effective in reducing skeletal related events (SREs) and minimizing BPs associated ONJ

4 MANAGEMENT AND STAGING OF BPS INDUCED ONJ

According to previous literature management strategies of BPs associated ONJ is mostly palliative and empirical.[26] BPs associated ONJ management started after advised morning fasting serum CTX test and begins palliative care. If the exposed bone is painless, treatment started with 0.12% chlorhexidine mouth rinse but if patient complaints pain and/or clinical evidence of infection, antibiotic therapy should be provided in addition to the 0.12% chlorhexidine. But invasive dental procedure is only indicated if the CTX value is greater than 150 pg/ml, to achieve, uncomplicated healing. [22, 27, 28]

Following treatment modalities of BPs associated ONJ was discussed in previous literature like: sequential removal of sequestra (conservative approach) and extensive involvement may necessitate large area of debridement to include

segmental mandibulectomy and partial maxillectomy[17], mandibular reconstruction with the fibula flap[29], cover the exposed areas with tissue flaps[16], Pentoxifylline with α-tocopherol reduces 74% area of bony exposure and symptom control[30], transplantation of intralesional autologous bone marrow stem cell[31], Hyperbaric Oxygen therapy[32, 33]. Each treatment modalities have own merit/demerit but no fixed treatment protocol was proposed before recent position paper published by AAOMS (2009).

Recently published position paper by AAOMS (2009), provide new staging and treatment strategies that is listed in **Table 2.**

TABLE -2

THE AAOMS STAGING AND TREATMENT STRATEGIES FOR BPS ASSOCIATED ONJ[4]

Staging	Treatment Strategies
At Risk Category: No apparent necrotic bone in patients who have been treated with either oral or IV BPs	❖No treatment indicated ❖Patient education
Stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms	❖Systemic management, including the use of pain medication and antibiotics
Stage 1: Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection	❖Antibacterial mouth rinse ❖Clinical follow-up on a quarterly basis ❖Patient education and review of indications for continued BPs therapy
Stage 2: Exposed and necrotic bone associated with infection as evidence by pain and erythema in the region of the exposed bone with or without purulent drainage	❖Symptomatic treatment with oral antibiotics ❖Oral antibacterial mouth rinse ❖Pain control ❖Superficial debridement to relieve soft tissue irritation
Stage 3: Exposed and necrotic bone in patients with pain, infection, and one or more of the following: ❖Exposed and necrotic bone extending beyond the region of alveolar bone, (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathological fracture ❖Extra oral fistula ❖Oral antral / oral nasal communication or ❖Osteolysis extending to the inferior border of the mandible of sinus floor	❖Antibacterial mouth rinse ❖Antibiotic therapy and pain control ❖Surgical debridement/resection for longer term palliation of infection and pain

5 CONCLUSION

BPs associated ONJ is a rare but serious clinical condition caused by antiosteoclastic, antiangiogenic and anti human endothelial cell proliferation effects of Bisphosphonates which inhibit bone turnover. They are commonly developed in those patients who receiving either long term nitrogen containing IV BPs therapy alone or associated with invasive dental procedure. Therefore proper dental evaluations and receive necessary treatment prior to initiating IV BPs therapy. Manipulation of IV BPs dosing may be effective in reducing skeletal related events (SREs) and minimizing BPs associated ONJ. CBCT and morning fasting CTX level are the useful assessment tool to predict risk and to make appropriate line of treatment. In cases of established disease management strategies is mostly palliative and empirical.

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