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BISPHOSPHONATE RELATED OSTEORADIONECROSIS OF JAW- A REVIEW

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ABSTRACT

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is an area of uncovered bone in the maxillo-facial region that did not heal within 8 weeks after identification by health care provider, in a patient who was receiving or had been exposed to Bisphosphonate Therapy (BPT) without previous radiation therapy to the craniofacial region. The management of BRONJ currently is a dilemma. No effective treatment has yet been developed and interrupting BPT does not seem to be beneficial. Temporary suspension of BPs offers no short-term benefit, whilst long term discontinuation (if systemic conditions permit it) may be beneficial in stabilizing sites of ONJ and reducing clinical symptoms. The use of oral antimicrobial rinses in combination with oral systemic antibiotic therapy -penicillin, metronidazole, quinolones, clindamycin, doxycycline, and erythromycin- is indicated for Stages I and II of Ruggiero's Staging. The role of hyperbaric oxygen therapy is still unclear but some benefits of this treatment have recently been described in association with discontinuation of BPT and conventional therapy (medical or/and surgical). Surgical debridement or resection in combination with antibiotic therapy may offer long-term palliation with resolution of acute infection and pain. Mobile segments of bony sequestrum should be removed without exposing unaffected bone. Ozone therapy in the management of bone necrosis or in extractive sites during and after oral surgery in patients treated with BPs may stimulate cell proliferation and soft tissue healing.

Key words: Osteoradionecrosis, Jaw, Bisphosphonate, Chemotherapy.

INTRODUCTION

Bisphosphonates: structure and mechanism of action

Bisphosphonates are the pyrophosphate analogue with a carbon substitution. Both P-C-P structure of bisphosphonate and P-O-P structure of pyrophosphate have strong affinity with calcium phosphate crystal and their bindings inhibit further calcium phosphate accretion or dissolution [1]. Their molecular mechanisms of action are thought to be the inhibition of bone resorption by direct effects on osteoclasts [2]. When osteoclasts form their resorption lacunae during the bone resorption, bisphosphonates, which have been incorporated into mineral surfaces, would be simultaneously sequestered and endocytosed into cells through their ruffle borders [3]. Two additional covalently bounded groups (side chains) attached to the geminal carbon atom in P -C - P group, referred to, as R1 and R2, allow for variations in structure [2]. When R1 is a hydroxyl (-OH) or primary amino (-NH2) group, the affinity to hydroxyapatite is enhanced. R2 is the determinant of antiresorptive potency. R2 containing aminonitrogen atom in an alkyl chain (as in pamidronate and aledronate) was found to be much more potent than non-nitrogen containing one (etidronate and clodronate) and the most potent forms were those containing a nitrogen atom within heterocyclic ring (as in risedronate and zoledronic acid) [4,5]. These findings led to the classification of bisphophonates into two main groups: nitrogen containing (nBP) or non-nitrogen containing (nnBP). Nitrogen-containing bisphosphonates inhibit farnesyl disphosphate synthase (FPP synthase): an enzyme active in the mevalonate pathway [6]. This FPP synthase inhibition in osteoclasts results in a reduced bone resorption through different dose-dependent ways.

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At a low concentration it inhibits the synthesis and formation of the cytoskeleton and thus impairs vesicular trafficking and membrane ruffling. At a higher concentration, it inhibits the osteoclast differentation and finally induces osteoclast apoptosis [7]. nBPs promote osteoclast apoptosis due to their conversion into methylene-containing adenosine triphosphate analogues. This inhibits critical adenosine triphosphate-dependent enzymes, particularly and significantly, the adenine nucleotide translocase of the mitochondrial transition pore complex, which is an important trigger causing apoptosis [8]. Osteoclast apoptosis is suspected to be the primary mechanism by which nnBPs suppress bone resorption [9,10]. The bisphosphonates become incorporated into newly formed ATP, because of their similarity to inorganic pyrophosphate (PPi) and this ATP cannot be hydrolysed. Intracellular accumulation of these non-hydrolyzable ATP analogues is believed to be cytotoxic to osteoclasts because they inhibit multiple ATP-dependent cellular processes, leading to osteoclast apoptosis [11]. The administration route of clodronate is intramuscular or oral or intravenous, for alendronate it is oral, and for pamidronate and zoledronate it is only intravenous [12].

Indications of bisphosphonates

They are mainly used to treat and prevent malignant hypercalcemia, skeletal-related events associated with bone metastasis secondary to solid cancer, and in management of the lesions of multiple myeloma, Paget's disease, primary and secondary hyperparathyroidism and osteoporosis [13].

Historical background of BRONJ

In 2002, the Food and Drug Administration (FDA) received first reports related to several patients with cancer, treated with the IV bisphosphonates (BP), who developed osteonecrosis of the jaw [14,15]. In 2003, Robert.E.Marx published the discovery of an extremely therapy resistant osteonecrosis of the jaw. Patient who suffered with this kind of ONJ had all received BP treatment for metastatic bone disease or osteoporosis. Marx, thus, concluded that there is a co-relation between BP therapy in this acute osteonecrosis of the jaws. This was not the first time that this condition was reported in medical literature, however the "phossy jaw" was first described in British medical journal in 1889 [16,17].

Phosphorus matches were first sold in the UK in 1827, creating a new industry of cheap lights but at high human cost. Breathing in phosphorus vapours led to the industrial disease phossy jaw which slowly ate away the jaw bones. This condition particularly affected the girls who made phosphorus matches. Finally, the year 1910 saw the birth of legislation prohibiting the use of white phosphorus in british match factories and instructing factory owners to use the safer yet more expensive red phosphorus instead [17].

Definition

In order to discrimate BRONJ from other conditions, The American Society for Bone and Mineral Research define BRONJ as follows : Patients may be considered to have BRONJ if they have all of the following criteria:

1) Current or previous treatment with a bisphosphonate;
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 [18].

However, stage 0 BRONJ, where there is no exposed bone is not compatible with the definition. Therefore an update of the definition was performed as "exposed or otherwise necrotic bone" [19].

Prevalence

The incidence of BRONJ remains undefined and it ranges from 0.8 to 12% for i.v. preparations; the incidence for oral preparations ranges from 0.01 to 0.06% and for oral invasive treatments this rate increases from 0.07 to 0.34%. BRONJ is more often localized in the mandible more than in the maxilla (2:1 ratio). It is usually caused by a dental surgical procedure (60-70% of the cases) or a prostheic trauma and it is more rarely spontaneous.

According to literature, BRONJ mainly affects people over 60 years of age and females more than males [20]. Several thousand cases of ONJ have now been reported in the literature, which were reviewed in 2010. Of 2,408 cases, 88% were associated with intravenous therapy, primarily with zoledronate alone or zoledronate sequentially with pamidronate, although 19% of this group had received pamidronate alone, 261 patients (11%) had only received oral bisphosphonates, in most cases alendronate. In 89% of the cohort, the underlying condition being treated was a malignancy, multiple myeloma in 43%, breast cancer in 32%, prostate cancer in 9% and other cancers in 5%. This distribution is probably a reflection of the cancers for which bisphosphonates are currently used. Of the 11% of the patients with a benign condition, most had osteoporosis. 61% of all patients were female, again probably reflecting the nature of the underlying conditions for which bisphosphonates are prescribed. 67% of cases were preceded by tooth extraction, whereas another factor, such as denture pressure sore or torus was identified in 7%; no predisposing factor was found in 26% of the patients. In the patients whose ONJ stage was reported at presentation, 16% had stage I disease (asymptomatic necrotic bone), 66% were at stage 2 (painful or infected necrotic bone), and 18% had stage 3 disease (extra-oral complications, extensive sequestration or pathological fracture) [21].

Longitudinal studies, involving a total of 7,500 patients have demonstrated an ONJ incidence of 2-11% associated with myeloma, 1-7% for breast cancer and 6-15% for prostate cancer (suggesting no considerable

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difference in incidence between these malignancies) and an overall prevalence of about 5%, consistent with findings from a medical claims database (5.5% prevalence at 72 months). The mean time to development of ONJ in cancer patients treated with zoledronate is 1.8 years but ranges from 6 to 60 months. As there seems to be an approximately linear relationship between duration of therapy and prevalence, it is likely that the overall prevalence of 5% will creep up as longer-term studies become available, unless changes in management practices can circumvent this [22].

Tools for diagnosis

1. Imaging : The radiographic features of BRONJ are not specific. Periapical and panoramic radiographs serve as an initial screening modality. CT and MRI provide a more comprehensive evaluation of the jaws and help to delineate the extent of the disease [23].
2. Periapical radiograph and cone beam computed tomography (CBCT): reveals generalized thickening of the cortical plate and lamina dura, mixed sclerotic and lytic bone destruction involving alveolar bone and basal bone, sequesters, encroachment on the mandibular canal and maxillary antrum and pathological fracture while thickening of cortical plate in the affected region was the only radiological findings of CBCT [24].
3. Computed tomography (CT) images: reveal sclerotic changes, osteolytic changes, periosteal bone proliferation, sequestration and inferior alveolar canal involvement while contrast enhanced magnetic resonance imaging (MRI) reveal intensity changes of the cortical and sub cortical bone structures, contrast enhancement in necrotic bone area, soft tissue involvement and cervical lymphadenopathy [25].
4. Bone scans: Three phase bone scans are used as a screening modality for patients with symptomatic or asymptomatic osteonecrosis. Bone scans can show abnormal radionuclide uptake 10-14 days before bone mineral loss significant for radiographic changes is seen on conventional films. This could make them more sensitive in detecting early subclinical BRONJ [26]. During the early stages of BRONJ, the uptake is reduced and as the disease progresses, the uptake is increased, consistent with increased osteoblastic activity [27]. Imaging could also enable the determination of the exact margins of bone resection during aggressive management of BRONJ. Tetracycline bone fluorescence has recently been used to visualize margins of the osteonecrosis more precisely, given that only viable, but not necrotic, bone fluoresces. Fluorescence-guided bone resection might improve the surgical therapy of osteonecrosis.
5. CTX: BRONJ has a wide variety on appearances on imaging, the diagnosis cannot be made from radiologic studies alone. It would be helpful for the diagnosis, treatment and prognosis to have objective means of evaluation. Serum collagen telopeptide (CTX) is a reliable index for evaluating the bone turnover rate and the antiresorptive therapy [28]. Whether the serum CTX value is as a good index to predict the risk of BRONJ is controversial. Marx et al. and other researchers found lower serum CTX values in patients with BRONJ [29,30]. In any event, CTX monitoring could help determine the best timing for a so-called “drug holiday” allowing the restoration of bone remodeling and healing capacity and improving the predictive outcome of BRONJ treatment. However, cancer patients are generally not eligible for drug discontinuation even if some clinical experience seems to support a long-term discontinuation of i.v. BPs in cancer patients when systemic condition allows [31].

Differential Diagnosis

Patients who are at risk of BRONJ or those with established BRONJ may also present with other common clinical conditions not to be confused with BRONJ. These conditions include, but are not limited to, avascular osteitis, osteomyelitis, osteoradionecrosis, sinusitis, gingivitis, periodontitis, caries, periapical pathology and temporomandibular disorders. Some of these conditions, such as periodontitis and periapical pathology could also contribute to the development of BRONJ in patients at risk. Osteoporosis may resemble BRONJ, presenting with an area of denuded avascular bone. However, osteoporosis can easily be differentiated from BRONJ by its classic radiographic appearance and by lack of history of BP exposure.

Risk factors

There are several risk factors for BRONJ that are categorized by American Association of Oral and Maxillofacial Surgeons (AAOMS) as follows:

1. Drug related risk factors

a) Bisphosphonate Potency: Since intravenous administration leads to a higher drug exposure than the oral route, osteonecrosis related to oral bisphosphonate therapy is less common than that of related to intravenous forms such as zoledronate which is also more potent than oral bisphosphonates [31]. Nitrogen containing bisphosphonates possess higher risk regarding BRONJ development than non-nitrogen containing bisphosphonates [32]. The higher incidence of alendronate associated osteonecrosis of the jaw was found as compared to other bisphosphonates, which may be related to the frequent prescription of alendronate, or can be explained by its dose, potency, half-time, and absorption related factors.

b) Duration of therapy: As oral bisphosphonates are less bio-available than intravenous formulations, they are used for long-terms. Longer duration (for more than two years) has been associated with an increased risk of oral BRONJ [33].

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2. Local risk factors: Dentoalveolar surgical procedures such as teeth extractions, periapical surgery, dental implant placement, and periodontal surgery involving osseous injury, as well as concomitant oral disease, poorly fitting removable dental prosthesis and poor oral hygiene are risk factors for BRONJ. Local anatomy also plays a part in the development of BRONJ. Lesions are more frequent in the mandible than maxilla and more common in bony prominences with thin mucosa; tori, bony exostoses and the mylohyoid ridge. Cancer patients exposed to i.v. bisphosphonates with a history of inflammatory dental disease e.g. periodontal and dental abscesses are at a seven-fold increased risk of developing BRONJ.

3. Demographic and systemic factors: Increased age (older than 65 years) was found to be a risk factor for BRONJ. Additionally, oral BRONJ is more common in women than in men. This is not an unexpected finding, since osteoporosis – particularly the postmenopausal type- is the primary indication for oral bisphosphonates. Some systemic factors such as renal dialysis, low haemoglobin, obesity, immunosuppression, rheumatoid arthritis, smoking, and diabetes were reported to increase the risk for BRONJ. Additionally, prednisone and methotrexate used in auto-immune diseases are associated with an additional inhibition of remodelling in oral bisphosphonate cases.

4. Genetic factors: Single nucleotide polymorphisms in the cytochrome P450-2C gene and IGF-1 genes may play part in the pathogenesis of BRONJ [34]. Sarasquete et al. demonstrated recently that CYP2C8 gene diversity influences the likelihood of development of BRONJ in multiple myeloma patients receiving bisphosphonate therapy [35].

5. Preventative factors: According to the recommendation of the AAOMS Taskforce on BRONJ, underlying dental evaluations and getting required treatment before being started on bisphosphonates may be effectual on decreasing the risk for BRONJ.

Pathogenesis

Exact pathogenesis of BRONJ is not known till today, but numerous hypotheses that promote and interlink the development of BRONJ are found in literature.A number of possible mechanisms of ONJ have been proposed [36-38].

1.Immunomodulation: Immunomodulation, including impairment of local immunity of the jaw bone and changes in immune and inflammatory responses may play an important role in the pathogenesis of ONJ. Local bisphosphonate concentrations or the resulting increase of IPP in the case of nitrogen-containing bisphosphonates may be possible factors responsible for immunosuppressive effects which allow the development of infections at ONJ sites. As bisphosphonates bind calcium, a release of bisphosphonates from the jaw bone, e.g. due to trauma or necrosis, could also lead to localised immunosuppression as some immunological reactions, such as the recruitment of T-lymphocytes and the expression of specific functional signals of dendritic cells, are calcium-dependent [39].

2. Infection: The presence of bacteria is an almost universal finding in histological samples of ONJ (Actinomyces). Yeast has also been identified in some patients. Biofilms, which are resistant to natural immunity and antibiotics, have also been found at ONJ sites. Bacteria may increase bone resorption and some bacteria may also inhibit bone formation. Bone coated with bisphosphonate may also increase bacterial adhesion through electrostatic interactions. A role for infection is further supported as the jaw is prone to trauma and bacterial contamination and there are reports of ONJ healing after antibiotic treatment. There is little evidence in the literature against a role of bacteria although some authors caution that bacteria in oral lesions would be expected in the micro-organism rich environment of the mouth. Infections may be a secondary complication that worsens the situation due to the reduced local immune response rather than the primary cause of ONJ [40].

3. Excessive reduction of bone turnover: Excessive reduction of bone turnover that may impair bone remodelling and repair has been proposed as a mechanism for ONJ. Bisphosphonates are known to reduce bone turnover and remodelling through inhibition of osteoclasts. This is supported by evidence from genetic conditions which affect osteoclast activity and thereby provide means of studying the effects of remodelling suppression. The requirement for remodelling may also be increased in the jaw following infection or dental procedures which are risk factors for ONJ. However osteonecrosis is rarely seen at sites other than the jaw (although this may be due to conditions unique to the jaw) and ONJ does not appear to occur in other conditions associated with reduced bone turnover such as hypoparathyroidism. There is also evidence that bone turnover may not be reduced in ONJ lesions as osteoclasts have been observed in ONJ lesions indicating active bone resorption at these sites [41].

4.Impaired angiogenesis: The anti-angiogenic effect of bisphosphonates has been proposed as a possible mechanism for ONJ either as an initiating factor or secondary to reduced bone turnover. Reduced blood supply may be of particular importance in wound healing following dental procedures. Bisphosphonates are known to inhibit vascular endothelial growth factor and formation of capillaries. In cases of ONJ, bisphosphonates may inhibit the building of new capillaries that lead into the bone however this anti-angiogenic effect is not seen in the soft tissue. However, ONJ occurs in both the maxilla which is well supplied with blood vessels as well as the mandible which has a more restricted vascular supply. Furthermore, ONJ has not been identified as a possible drug safety signal in association with other anti-

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angiogenic drugs although combination treatment of bisphosphonates with other anti-angiogenic drugs (e.g. glucocorticoids, chemotherapy) may have a synergistic effect in the pathogenesis of ONJ.

5.Bisphosphonate toxicity to soft tissue: Bisphosphonate toxicity to the soft tissue may result in suppression of cell proliferation, mucosal thinning and reduced healing in the oral mucosa which spreads into adjacent bone. Sites with elevated bone turnover are expected to have increased bisphosphonate concentrations which may lead to the release of bisphosphonate from bone into the surrounding oral mucosa. Bisphosphonates are known to be toxic to epithelial cells and oesophageal erosions and ulcers are recognized side-effects. In addition, zoledronate has been demonstrated to induce apoptosis in oral fibroblasts and epithelial cells and there is evidence from *in vitro* studies that the presence of osteoclasts may increase the release of bisphosphonates from bone. However some authors have suggested that in cases of ONJ, bone damage may be present before soft tissue damage occurs [42].

6. Direct bisphosphonate toxicity to bone: At high concentrations in bone, bisphosphonates may be toxic to other bone cells as well as osteoclasts. Bisphosphonate concentration may be higher in the jaw and inhibition of the FPPS enzyme affected by nitrogen-containing bisphosphonates can cause apoptosis in any cell. However generalized bone toxicity is not seen with bisphosphonates. The effects of bisphosphonates in the microenvironment may be dependent on the local concentration of bisphosphonate. For IV bisphosphonates the high concentration of bisphosphonate in the blood achieved during the infusion may enable bisphosphonates to enter other cells in addition to osteoclasts and the duration of IV infusion may have important clinical effects.

7. Other proposed mechanisms: Other mechanisms for bisphosphonate-induced ONJ have been proposed including hypocalcaemia and secondary hyperparathyroidism, uncoupling of the osteoblast-osteoclast equilibrium [43], metastasis and synergistic effects with other drugs such as chemotherapy and corticosteroids and concurrent diseases. Genetic factors have also been implicated and Matrix Metalloproteinase 2 (MMP) and Rs1934951 polymorphism on CYP2C8 have been proposed as possible candidate genes [44,45]. Recently, a review was published on influence of acidification of the microenvironment on the release of bisphosphonates from hydroxyapatite. This alleged decrease in pH caused by tissue ischemia, and hypoxia in diabetes, wounding, inflammation, and infection or because of uncontrolled H^+production by cells in rapidly growing tumors result in an increased release of bisphosphonates, to a toxic level which eventually may result in BRONJ [46].

Skeletal site-specific differences

It is quite remarkable that BRONJ almost exclusively occurs in the jaw. The reasons thought to be, are the greater degree of vascularisation and the daily remodelling that occurs around the periodontal ligament of the teeth. In addition, the chronic nature of invasive dental disease, and the treatment it requires occurs in a location where adjacent bone is minimally protected by a thin mucosal covering [47]. Axial and appendicular bones remain rather unaffected. This leads towards another possible explanation: skeletal site-specific cellular differences form the basis for BRONJ of the jaw. Data presented in the literature indicate the existence of phenotypical differences between bone cells in orofacial bone compared to iliac crest bone. One of those differences is the lack of similarity in the response of mandible and iliac crest bone marrow stromal cells to bisphosphonate therapy. Compared to the iliac crest, mandible bone marrow stromal cells were less sensitive to bisphosphonates, but they promoted osteoclast differentiation of hematopoietic stem cells more than iliac crest bone marrow cell in the presence of bisphosphonates [48]. This might point towards a difference in cell development and maybe related to a different embryological origin [49]. The maxilla and mandible develop from neural crest cells, while axial and appendicular bones are of mesodermal origin. Not only differences are found with respect to the response to bisphosphonates, but also site-specific differences exist in osteoclast populations. Everts *et al.* showed that osteoclastic resorption of calvaria bone (the upper, domed part of the skull) depends on activity of both cysteine proteinases and matrix metalloproteinases (MMPs), whereas long bone resorption depends on cysteine proteinases, but not on the activity of MMPs [50-52]. Furthermore, significantly higher levels of cathepsins B and K were expressed by long bone osteoclasts than by calvaria osteoclasts. These and numerous other data indicate phenotypic differences between osteoclast populations. Whether these different osteoclasts respond differently to bisphosphonates has not been elucidated yet [53].

Management

Although the literature on ONJ is rapidly evolving, most of the evidence to date is in the form of retrospective case studies and case series. A Canadian dental group have, therefore, developed consensus-based clinical practice guidelines for the diagnosis, prevention and management of bisphosphonate-associated ONJ [54,55]. As the authors acknowledge, the evidence base for the guidelines was drawn from collective multidisciplinary expert opinion due to the paucity of high-quality data from clinical trials.

The guidelines have been endorsed by a number of diverse societies representing stakeholders in the dental field (e.g. the Canadian Association of Oral and Maxillofacial Surgeons), bone field (e.g. the International Bone and Mineral Society) and the field of diagnostics (e.g. the International Society of Clinical Densitometry). The guidelines complement the recommendations of the American Society for Bone and Mineral Research task force.

Prevention of BRONJ in patients with or without risk factors

The task force made the following recommendations based on collective clinical experience:

(a) In all patients receiving bisphosphonate therapy, physicians should stress the importance of maintaining good oral hygiene.

(b) Lifestyle changes, such as stopping smoking and limiting alcohol intake, should be encouraged in patients at high risk for ONJ.

(c) In all cases, physicians are highly encouraged to discuss the very rare occurrence of ONJ (including risk factors and prevention strategies) with patients in whom they have recommended a bisphosphonate for non-cancer indications. For cancer patients receiving high-dose frequent IV bisphosphonate therapy, where the risk for ONJ appears to be substantially higher, more specific information should be provided.

For oncology patients prescribed high dose i.v. bisphosphonate therapy:

(a) Prior to the initiation of IV bisphosphonate therapy in the oncology patient, a thorough dental examination, including radiographs, should be completed.

(b) In oncology patients, if any invasive dental procedure (e.g., tooth extraction, surgery) is deemed necessary, it should be completed and optimal dental health achieved prior to initiating bisphosphonate therapy if the patient's medical condition permits the delay [56]. This would apply to the pediatric population, as well.

(c) For oncology patients receiving IV bisphosphonate therapy who require an urgent invasive dental procedure, it is recommended that the procedure be completed and interruption of bisphosphonate therapy be considered during the healing period, if the medical condition permits. If the procedure is non-emergent, it is recommended that one consider interruption of the bisphosphonate for 3 to 6 months prior to the procedure, and until the surgical site has healed, if the medical condition permits. While this may be difficult in patients at high risk for hypercalcemia of malignancy, other non-bisphosphonate options should be considered for the short-term medical management of these patients.

For the osteoporosis patients prescribed oral or i.v. bisphosphonate therapy:

(a) For the osteoporosis patient expecting to receive oral or IV bisphosphonate therapy who has practiced appropriate preventive dental care and reports no acute dental problems, routine follow-up dental examinations are appropriate. If appropriate dental care has not taken place, or if there is an acute dental problem, this should be addressed prior to initiating a bisphosphonate. As is recommended for all individuals, patients taking bisphosphonates should maintain good oral hygiene practices and attend semiannual dental examinations [57]. In osteoporosis patients receiving an oral or IV bisphosphonate who present with a true dental emergency, invasive surgery should not be delayed. Consideration should be given to interrupting the bisphosphonate during the healing period.

(b) For the osteoporosis patient requiring non-emergent invasive dental surgery, interruption of bisphosphonate therapy for several months prior to the procedure and throughout the healing period may be considered. However, there are no clinical trial data to guide the duration of cessation of therapy; and it should be emphasized that, at present, only anecdotal data exist to suggest discontinuing a Bisphosphonate reduces risk. Clearly, implementation of the above guidelines is dependent upon the type and extent of dental coverage a given patient may have. As the relationship between bisphosphonate use and ONJ in the patient with osteoporosis remains unproven, it is not recommended that bisphosphonate therapy be withheld for osteoporosis if a patient is unable to be in full compliance with these guidelines in the absence of other major risk factors for ONJ. Delaying the initiation of bisphosphonate therapy pending a dental evaluation rarely would seem necessary in the osteoporosis patient. As bisphosphonates have longterm skeletal retention, it is not known if stopping treatment will alter the course of any ONJ lesions. No prospective data exist to address this question, but there are anecdotal reports of patients in whom ONJ seemed to resolve with appropriate dental care and cessation of the bisphosphonate, suggesting that cessation of the drug is reasonable [58]. Certainly the cessation of Bisphosphonate therapy for several months does not seem to have a detrimental effect on osteoporosis management [59].

Staging and treatment strategies for bisphosphonate-associated ONJ

AAOMS proposes use of the following revised staging system and appropriate management strategies:

1.Patients at risk

No apparent necrotic bone in asymptomatic patients who have been treated with IV or oral bisphosphonates.

2.Stage 0

Patients with no clinical evidence of necrotic bone, but present with non-specific symptoms or clinical and radiographic findings, such as,

• odontalgia not explained by an odontogenic cause

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•dull, aching bone pain in the body of the mandible, which may radiate to the temporomandibular joint region
• sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall
• altered neurosensory function

Clinical Findings
• loosening of teeth not explained by chronic periodontal disease
• periapical/periodontal fistula that is not associated with pulpal necrosis due to caries

Radiographic Findings
• alveolar bone loss or resorption not attributable to chronic periodontal disease
• changes to trabecular pattern—dense woven bone and persistence of unremodeled bone in extraction sockets
• thickening/obscuring of periodontal ligament (thickening of the lamina dura and decreased size of the periodontal ligament space)
• inferior alveolar canal narrowing
These non-specific findings, which characterize Stage 0, may occur in patients with a prior history of Stage 1, 2, or 3 diseases who have healed and have no clinical evidence of exposed bone.
3.Stage 1
Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection.
4.Stage 2
Exposed and necrotic bone in patients with pain and clinical evidence of infection.
5.Stage 3
Exposed and necrotic bone in patients with pain, infection, and one or more of the following:
• exposed 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
• pathologic fracture
• extra-oral fistula
• oral antral/oral nasal communication
• osteolysis extending to the inferior border of the mandible or sinus floor

Treatment strategies

At risk - Patients who are at risk of developing BRONJ by virtue of the fact that they have been exposed to a bisphosphonate do not require any treatment. However, these patients should be informed of the risks of developing BRONJ, as well as the signs and symptoms of this disease process.
Stage 0 – Provide symptomatic treatment, and conservatively manage other local factors, such as caries and periodontal disease. Systemic management may include the use of medication for chronic pain and control of infection with antibiotics, when 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. It is hypothesized that the pathogenesis of BRONJ may be related to factors adversely influencing bone remodeling. Additionally, BRONJ is not due to a primary infectious etiology. Most of the isolated microbes have been sensitive to the penicillin group of antibiotics. Quinolones, metronidazole, clindamycin, doxycycline and erythromycin have been used with success in those patients who are allergic to penicillin. Microbial cultures should also be analyzed for the presence of actinomyces species of bacteria. If this microbe is isolated, the antibiotic regimen should be adjusted accordingly. In some refractory cases, patients may require combination antibiotic therapy, long-term antibiotic maintenance, or a course of intravenous antibiotic therapy.

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.

Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.

A removable appliance may be considered to cover and protect the exposed bone. Additionally, a protective stent may be of benefit for patients with exposed bone that causes trauma to adjacent soft tissues and for patients in whom the osteonecrotic site is traumatized repeatedly during normal oral function. Either a thin, vinyl, vacuformed mouth guard or thin acrylic stent may be used, provided that the device does not further traumatize the osteonecrotic site and that it can be maintained hygienically by the patient [60].

Discontinuation of bisphosphonate therapy IV bisphosphonates

Oncology patients benefit greatly from the therapeutic effects of bisphosphonates by controlling bone pain and the incidence of pathologic fractures. Discontinuation of IV bisphosphonates offers no short-term benefit. However if systemic conditions permit, long-term discontinuation may be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development and reducing clinical symptoms [61]. The risks and benefits of continuing bisphosphonate therapy should be made only by the treating oncologist in consultation with the Oral and maxillofacial surgeon and the patient.

Oral bisphosphonates

Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease. Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution following debridement surgery. If systemic conditions permit, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient. Suggested additional therapies for BRONJ include hyperbaric oxygen, parathyroid hormone, platelet rich plasma and lasers [62-64]. Since hyperbaric oxygen is known to decrease edema and inflammation, enhance microbial killing, vasculogenesis and tissue repair in wounds, it can improve wound healing and pain scores when added to surgical and non-surgical protocols [65].

The efficacy of parathyroid hormone in BRONJ mostly depends upon its ability to elevate suppressed bone remodeling associated with bisphosphonates. However, its use in patients with metastatic cancer should be considered meticulously as it may promote skeletal metastases [66-69]. Some authors have reported the beneficial effect of low level laser therapy to reduce the BRONJ related pain and inflammation. The efficacy of these additional therapies should be established entirely by further researches [70].

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 cannot be neglected. An oral health program in terms of oral hygiene methods and routine dental care is considered as the most favourable approach for patients receiving bisphosphonate therapy. Stopping smoking and limiting the alcohol intake are also recommended.

Patient education in terms of the symptoms and initial signs of BRONJ is essential. Detailed regular intraoral examinations are crucial for detecting the early stages of BRONJ lesions. In cases on oral bisphosphonates and with concomitant risk factors, avoiding invasive dental surgery when possible, is also recommended. It is of great importance for physicians dealing with osteoporosis such as physiatrists, endocrinologists, and rheumatologists to be aware of the potential risk of developing BRONJ in patients on oral bisphosphonates and to work in accordance with dentists.

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