Bisphosphonates and osteonecrosis: an open matter

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Summary

Osteonecrosis of the Jaw (ONJ) in patients on long-term Bisphosphonate Therapy (BPT) is being reported in the last ten years in the literature with increasing frequency. The therapy for this condition is a real dilemma. Temporary suspension of BPT offers no short term benefits, hyperbaric oxygen has no proven efficiency and therefore is not recommended, intermittent or continuous antibiotic with surgical debridement can be beneficial to palliate the symptoms. Er:YAG laser can be used to eliminate necrotic portions of the bone by partial or total resection of the jaws as an alternative to conventional rotary tools. The high degree of affinity of this wavelength for water and hydroxyapatite means the soft tissue and bone can both be treated. The technique can also be used for conservative interventions by gradually evaporating the part of necrotic bone, getting close to the healthy area. One certain advantage of the Er:YAG laser is its bactericidal and biostimulatory action, inducing the healing of the soft tissues and the bone, quicker than in conventional treatments. In conclusion, from our experience, it is possible to observe that an early conservative surgical approach with Er:YAG laser associated to biostimulation, LLLT (Low Level Laser Therapy), for BRONJ could be considered as more efficacious in comparison to medical therapy or other techniques.

KEY WORDS: osteonecrosis of the jaw; bisphosphonates; bone surgery; laser; biostimulation; low level laser therapy; laser surgery.

Clinical findings of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)

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 (1). Moreover another variant of the disease represented by nonexposed BRONJ has been illustrated in the literature with high clinical impact (2, 3). Ruggiero in 2006 proposed a stage classification based on clinical symptoms. Stage I is represented by asymptomatic exposed bone necrosis, frequently discovered during a dental routine examination. Stage II has the same clinical features but it shows symptoms: swelling, abscess, pain, and inferior **alveolar nerve paresthesia**. Stage III is characterized by jaw fracture, maxillary sinus involvement or osteolysis extending to the inferior border of the mandible (Table 1).
Bone lesions can be observed in the mandible (65%) (especially in the mylohyoid ridge) and in the maxilla (26%) (particularly in the middle of palate and in the alveolar ridges). In 9% of the reported cases both mandible and maxilla are involved. BRONJ can be visualized using panoramic radiography, computed tomography (CT) and magnetic resonance imaging (MRI), although the extension of these lesions is not always clear, especially at the early stages.

Epidemiology and risk factors

Two different categories at BRONJ risk were identified: cancer and non-cancer patients. Low-grade risk of ONJ is connected with oral BPT used for treatment of osteopenia, osteoporosis and Paget's disease (from 0.01 to 0.04%) while higher-grade risk is associated with intravenous (IV) administration in the treatment of multiple myeloma and bone metastases (from 0.8% to 12%) (4, 5). The type and the dose of bisphosphonate (BP) must play a role in the initiation of ONJ: the *in vitro* activity on the inhibition of bone resorption (relative potency) varies from 1 for etidronate, to >10,000 for zoledronate. Nitrogen-containing drugs or aminobisphosphonates (N-BPs), have also been shown to have antiangiogenic and anticancer effect.
The effective dose of BP is 4 to 12 times higher in the metastatic cancer population than in patients treated for osteoporosis. BPs are drugs with long-term skeletal retention and it is unknown if stopping treatment will alter the course of ONJ lesions. These drugs accumulate in the bone matrix and are released over protracted time periods, months to years. The total doses and the duration of BPT directly influence the degree of which incorporation and release (6).
These drugs produce suppression of bone turnover and inhibits the ability to repair bone microdamage and is accumulated in bone in concentration sufficient to be directly toxic to the oral epithelium. BPs are also known to exhibit anti-angiogenic property with inhibition of vascular endothelial growth factor and formation of new capillaries. This process is more accentuated in the jaw bones with high vascularity and bone turnover (7). Oral epithelial cells are subjected to local increases in BP concentration after a traumatic event and that the presence of such BPs may inhibit normal epithelial wound healing, thus contributing to persistent exposure of underlying bone and the development of ONJ (8). Alendronate and risedronate inhibit epithelial cell proliferation *in vitro* by means of inhibition of farnesyl diphosphate synthetase, the same enzyme which is the target of BPs in osteoclasts. The cli-

Table 1 - Clinical classification of BRONJ by Ruggiero (2006) and successive modifications by AAOMS 2009.

BRONJ STAGE	DESCRIPTION	TREATMENT STRATEGIES
AT RISK CATEGORY	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment Patients education
STAGE 0	No clinical evidence of necrotic bone, but non specific clinical findings and symptoms	Systemic therapies including pain medications and antibiotics
STAGE I	No-symptomatic lesions with bone exposure in absence of infection's signs	Topical antiseptic therapy Follow-up
STAGE II	Bone exposure with pain, infection and swelling in the lesion's area	Oral antibiotics - antibacterial mouth rinse - pain control Superficial debridement to relieve soft tissues irritation
STAGE III	Bone exposure, pain, inflammation, maxillary sinus involvement, cutaneous fistulas and pathological fractures	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement and resection for longer term palliation of infection and pain

Modified from: "AAOMS (American Association of Oral and Maxillofacial Surgeons): Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws – 2009 update. J Oral Maxillofac Surg 2009;67:2-12".

nical sequelae of this phenomenon are well recognized in the form of upper gastrointestinal side effects from bisphosphonate use and also as oral ulcerations occurring in patients in oral BPT (9).
Comorbidities, steroid and antiangiogenic factors use along with BPs may cause ONJ to occur sooner, be more severe, and respond more slowly to a drug discontinuation (10).
The surgical trauma is a recognized predisposing factor to ONJ development but the spontaneous forms (probably connected to endodontic or periodontal infections) are reported with significant percentages in the literature (>40%) (11).

BRONJ management

There is general agreement in the literature on the fact that dental preventive measures in patients being candidate for or already receiving BPT are extremely important to reduce the risk of BRONJ development.
The BRONJ management is controversial: there are no evidence-based guidelines in the literature, in particular regarding surgical procedures, with good results for a long-term follow-up (12).
The first objective of each treatment is to alleviate pain, reduce infection and stabilize the progression of disease and the literature privileges the non-invasive approach above all for asymptomatic stages of BRONJ (Stage I in Ruggiero staging) (Table 1).
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 position paper of AAOMS suggested the use of oral antimicrobial rinses for stage I and systemic antibiotic therapy (penicillin, metronidazole, quinolones, clindamycin, doxycycline, erythromycin) for symptomatic stages (stages 0, II and III) (Table I) (13).
The main difficulty of local or systemic antibacterial therapy is the temporary clinical result with abscess, pain, and swelling improvement which is yet followed after an average of three weeks by a relapse of infection and symptoms. The first problem is that these patients old or undergoing chemotherapy, are debilitated by their malignancy, and are thus not able to bear the side effects of prolonged (and sometimes permanent) therapeutic antibiotic schedules. The second problem is represented by the possible evolution of disease and the uncontrollable passage from stage I to advanced stages of BRONJ (14).
Recently teraparatide (N-terminal 34 amino acids of recombinant human parathyroid hormone) was reported for medical treatment of BRONJ. This compound increases bone density stimulating osteoblastic bone formation and stimulates bone remodelling, but the treatment could be limited to 2 years because preclinical studies shoved the risk of osteosarcoma for long-term exposure. For these reason teriparatide is not recommended for patients with metastatic cancer for the risk of exacerbation of bone metastasis (15, 16).
Pentoxifylline and α-tocopherol in addition to antimicrobial therapy induced a 74% decrease in area of bony exposure and symptoms in BRONJ patients also in early stages of disease (17).
In vitro studies support the hypothesis that local or systemic treatment with Geranylgeraniol (GGOH) improves viability and migration capacity of osteoblasts, fibroblasts and endothelial cells with possible mucosal healing also in stage I of BRONJ (18).
Ozone therapy (OT) and Hyperbaric Oxygen Therapy (HBO) may stimulate cell proliferation and soft tissue healing reducing pain (19, 20). Laser applications at low intensity (Low Level Laser Therapy - LLLT) have been reported in the literature for the treatment of BRONJ. Biostimulant effects of laser improve reparative process, increase inorganic matrix of bone and **osteoblast mitotic index** and stimulate lymphatic and blood capillaries growth (21, 22). OT, HBO, LLLT are in general recommended in addition to medical or surgical therapy: frequently the positive clinical result is due to an improvement of traditional treatments by these alternative therapies.
Surgical jaw bone 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 and necrotic tissue should be removed extending surgery until unaffected bone. In diffuse BRONJ the resection of mandible and vascularized reconstruction with free fibula flaps are proposed in the literature (23). In the case of large and complex surgical interventions a careful evaluation of the general conditions of each patient shall be needed, including situation and evolution of disease, age, performance status and life expectancy.
The position paper of AAOMS suggested to limit surgical procedures to Stage III only, but many successive studies reported very good results of surgery also in early stages of BRONJ.
At this moment there is no consensus concerning an ideal treatment for stage I of BRONJ and no effective unique therapy has yet been developed. The non-invasive management of these con-

dition is related to the prevention of the possible extension of the necrotic process, but many authors reported better results with surgical therapy than with medical treatment only and proposed an implementation of surgical procedures, in the cases uncontrolled by local or general therapy, to avoid the risk of evolution to stage 3 (24).
The erbium laser surgical technique provides the opportunity to perform bone resection of the upper and lower jaw affected by BRONJ even under local anaesthesia. Surgical debridement can also be performed, by gradually evaporating the portion of necrotic bone at increasing depths close to the healthy bone. The minimally invasive technique of evaporation allows the sectioned bone surfaces to be made regular and can be used to create micro-perforations at the base for renewed vascularisation. The additional advantages of laser therapy are represented by the bactericidal and biostimulatory action of the laser beam with a better post-operative recovery (25-27).

Conclusions

The BRONJ therapy remains an unresolved problem and there are no evidence-based guidelines. In each patient affected by BRONJ or under BPT it is mandatory to obtain informed consensus to treatment. The counselling will be including risk rate of treatment, possible alternatives, consequences, the non foreseeable result of invasive dental procedures or BRONJ treatment and necessity of dental follow-up.
On the basis of recent literature it is necessary to consider the treatment of patients affected also by early BRONJ stages with combined conservative surgical strategies to obtain a greater control of these lesions for longer periods of time. The previous considerations support the hypothesis that the medical therapy and alternative non-invasive therapies (LLLT, OZ OTI) can be effective in jawbone and mucosa defects connected to BRONJ development. Moreover, minimally invasive surgical treatment (eventually laser-assisted surgery) nowadays appears to be a promising approach for BRONJ management.

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