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Clinical Healthcare Protocol for Bisphosphonate Related Osteonecrosis of the Jaw

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Introduction

In 2007, the World Health Organization (WHO) and in 2009 the AAOMS (American Association of Oral Maxillofacial Surgery) defined BRONJ (bisphosphonate-related osteonecrosis of the jaw) as "exposed bone in the maxillofacial region that has persisted for more than eight weeks in patients treated with bisphosphonates (BPs) with no history of radiation therapy to the jaws", and divided the disease into four stages based on morbility: Stage 0, evidence of radiologic findings; Stage 1, presence of clinical signs; Stage 2, presence of signs and symptoms; Stage 3, involvement of associated structures: bucco-nasal communication, cutaneous fistula, anesthesia of the inferior dental nerve and pathological fracture". (1)

In 2014 the AAOMS recommended that the nomenclature of "BRONJ" (bisphosphonate-related osteonecrosis of the jaw) be modified to "MRONJ", taking into account the existence of other drugs such as denosumab (monoclonal antibody) that could cause the same incidence of BRONJ, both in osteoporosis and in cancer treatments (2). However, there are no prospective dental studies expressly indicating the incidence of "MRONJ" in patients treated solely with monoclonal antibodies. This report will focus on BRONJ.

BPs are synthetic pyrophosphate analogs that cannot be degraded by pyrophosphatases, are capable of fixing to the bone and inhibiting osteoclast function, and interfere with the bone resorption/neoformation balance and are used for the treatment of skeletal disorders (3) These drugs are prescribed for the treatment of skeletal disorders: osteoporosis, Paget's disease, osteogenesis imperfecta, fibrous dysplasia, hypercalcemia (multiple myeloma, breast cancer, prostate cancer). (4)

The FDA (Federal Drug Association) has established that BPs are safe drugs, and that at present 93% of MRNOJ are associated to chronic, high-dose treatments in cancer patients. (1)

Regarding this point, an incidence of 31.5% of BRONJ (stage 2 followed by stage 3 disease) was found in a prospective study which evaluated 25,538 patients between January 2007 and December 2013 at the Department of Bucco-Maxillofacial Surgery and Traumatology II of the University of Buenos Aires, Argentina (FOUBA).

CTX (β cross lap) titration has proved to be the most effective and specific marker known to date for the assessment of bone remodeling (5). It has been suggested that this assay would be useful in patients receiving BPs to evaluate their risk of developing BRONJ prior to an invasive osseous dental procedure. (6) However, CTX levels did not in themselves reflect the bone remodeling process (7), thus biochemical assays would not constitute a valid means of predicting the risk index for BRONJ associated to chronic treatment with BPs (2). This study did not reveal a significant decrease in CTX levels in patients with BRONJ compared to patients receiving BP therapy who did not develop the pathology. This fact would determine that CTX levels are not an effective BRONJ predictor for the therapeutic management of

patients under chronic BPs treatment. An evident relationship with Vitamin D (25 OH cholecalciferol) values was found as there is Vitamin D insufficiency with BPs intake.

Clinical Care Protocol for BRONJ

• Dental surgery: Patients treated with BPs may undergo plastic restorations without any problem providing the complete caries is removed and the septic focus totally eliminated (8).

• Endodontics: There is no scientific evidence consolidating its relationship with BRONJ. Faced with the possibility of performing endodontic treatment instead of dento-maxillary or maxillo-facial surgery, it would be advisable to opt for this non-invasive option, thus preventing the risk of BRONJ. Apicectomies are an absolutely contraindicated endodontic procedure in patients with BRONJ (8).

• Prosthodontics: In edentulous patients, with poorly-fitting, full removable prostheses, the presence of a traumatic chronic lesion on the bone crests may lead to the development of BRONJ; the same holds true for lesions on mandibular or palatine tori and on the mylohyoid line. Care should be also taken with patients who have partial removable prostheses with retainers or disadapted prosthetic bases that produce chronic traumatic ulcers, among others. These situations are considered risk factors for BRONJ through the stimulation of inflammatory mediators (9).

• Periodontics: A periodontic evaluation and eventual treatment is mandatory in patients with a diagnosis of chronic periodontitis before treatment with BPs; only supragingival scaling in those receiving treatment with BPs should be performed in order to avoid infectious exacerbation, thus avoiding a risk factor for the development of BRONJ. Periodontal surgeries are absolutely contraindicated. (10).

• Children: There are no references in the literature detailing BRONJ in pediatric patients treated chronically with BPs for pathologies such as osteogenesis imperfecta. However, due to the decrease in microcirculation produced by BPs, atraumatic bone treatment is essential in these patients (10)

• Orthodontics: BPs, according to their pharmacodynamics, would supposedly prevent the orthodontic displacement of teeth within the maxillary space, increasing the risk of BRONJ (9). Surgeries related to this speciality are strictly contraindicated.

• Bucco-Maxillo-Facial Surgery and Traumatology: The BRONJ Task Force of the ASMBR (American Association of Mineral Bone Research) in 2007 and the AAOMS in 2009 established a guideline for surgical care (5).

Treatment of BRONJ is conservative, with the administration of antiseptics, painkillers, and antibiotics as palliative therapy until the spontaneous exfoliation of the bone sequestration, a situation which provokes the absence of a mechanical stimulus in the patient, thus preventing the volumetric growth of the necrotic lesion (11). BRONJ are regarded as an aseptic necrosis and hence it is not advisable to perform biopsies (except in oncology patients for the differential diagnosis of malignant hypercalcemias); once the sequestration has exfoliated, the bone specimen should be studied by the anatomo-pathologist through demineralization. In a recent report by Paparella ML, et al of 24 cases, lamellar bone trabeculae were thicker (bone sclerosis), there were no osteocytes in the lacunae (bone necrosis), and there was a Paget-like structure with marked signs of bone remodeling and formation of multiple trabecular compartments that were not connected to the trabecular surface. The Paget-like trabecular structure would result in a loss of trabecular vitality and in the onset of an inflammatory process due to microbial invasion. (12).

It is further recommended that the patient perform lesion antisepsis through regular mouth rinses or irrigation (in the presence of mucosal fistula) with chlorhexidine 0.12%, povidone iodine 10% and rifamycin 0.05% (13) alternating these monthly. In cases of painful symptoms, painkillers, preferably NSAIDs (Ibuprofen, Naproxen, Flurbiprofen, Diclofenac, etc) should be administered. Antibiotics (amoxicillin 500 mg with clavulanic acid 125 mg, metronidazole 500 mg, and ciprofloxacin 500 mg) should be administered only in cases of BRONJ lesion exacerbation. Antibiograms are not applicable for determining correct BRONJ treatment as the bacterial flora found during microbiological culture correspond in the vast majority of cases to the habitual pathogenic buccal flora: Phorphyromonas gingivalis and Actinomyces actino-mycetemcomitans (14). Antibiotic prophylaxis is therapeutically meaningless as BRONJ do not pose a threat for bacterial endocarditis, except when the patient is reached by the American Heart Association protocols for presurgical prescription.

The AAOMS proposes a surgical approach for stage 3 patients: resection with rigid fixation placement; resection with delayed placement of rigid fixation; resection with or without rigid fixation with flaps for soft tissue replacement; resection and replacement of necrotic tissue with soft tissues flaps (2).

The use of the hyperbaric chamber (HBO2), (15), ozone therapy, or platelet-rich plasma (PRP) (16) do not appear to provide any benefit to patients with BRONJ.

Both the Canadian Consensus Practice Guidelines for Bisphosphonate-Associated Osteonecrosis of the Jaw of 2008 and the AAOMS in 2014 proposed that dental implant therapy is contraindicated in patients undergoing BPs therapy. The peri-implant bone undergoes continuous remodeling in the bony tissue-implant interphase, causing the long-term possibility of future BRONJ lesions.

They also exclude the "wait and see" approach in clinical situations in which sepsis becomes generalized provoking the exacerbation of infectious foci, affecting the patient's systemic health, in which case surgical treatment should be chosen to eliminate the septic foci in question.

Conclusion

It is essential that patients with BRONJ be treated in an interdisciplinary fashion.

The patient's stomatognathic system should be examined preventatively prior to the initiation of BPs treatment in order to avoid pathological buccal manifestations, following the same healthcare clinical protocols used for patients receiving head and neck radiotherapy.

Additionally, patients should be informed of the precautions to be taken, including regular dental appointments for oral health assessment. The risk of developing BRONJ should be evaluated according to the type of BPs administered and treatment duration (emphasizing the increased risk after three years of BPs therapy since BP accumulate intraosseously without metabolizing and increase exponentially to the detriment of bone remodeling). A thorough and complete evaluation of the patient´s clinical history should be performed to identify any additional systemic risks.

In patients diagnosed with BRONJ, it is essential to avoid manipulating the maxillary bone tissue which could lead to the volumetric expansion of the lesion, unless it is expressly required by the patient´s oncologist in order to rule out possible maxillary bone metastases or if the septic foci threaten the patient's systemic health.

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