The Challenge for the Dental Community-Bisphosphonate-Related Osteonecrosis of the Jaw

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Introduction

Bisphosphonates are a synthetic analogue of inorganic pyrophosphates, a potent inhibitor of osteoclast activity. They are used for the treatment of diseases characterized with a high level of bone resorption/multiple myeloma, osteolytic bone metastases, Paget’s disease of bone, fibrous dysplasia, McCune-Albright syndrome, hypercalcaemia of tumour origin, etc. They feature slow intestinal absorption; they are excreted by the kidneys and have high affinity to hydroxyapatite crystals. They incorporate into skeletal bones without being degraded. Bisphosphonates attach to calcium in areas of high bone resorption and remain integrated in the bone for more than ten years/for example, the half-life of Alendronate is 12 years. Once administered, they trigger a cascade of biochemical processes resulting in loss of the ability of osteoclasts to resorb bone, or even to apoptosis of osteoclasts.

Bisphosphonate therapy may cause some adverse effects/ kidney failure, arthralgia, fever, muscle pain, hypocalcemia and others. Bisphosphonate-related Osteonecrosis of the Jaw (BRONJ) is a severe, group-specific complication associated with the use of bisphosphonates. Most reported cases were caused by intravenous administration of bisphosphonates. There are a few case reports of osteonecrosis of the jaw caused by continuous oral administration. Marx RE [1], was the first to report 36 cases of “painful bone exposure of the lower and upper jaw in patients treated with bisphosphonates - pamidronate and zoledronate”.

Definition

Necrosis of the jaw bone, related or unrelated to dental procedures, persisting for more than six to eight weeks, refractory to conservative treatment, in patients without history of prior radiotherapy in the affected area, but treated with intravenous amino-containing bisphosphonates for at least one year, or orally - for a much longer period, for a general disease causing bone resorption.

Mechanism of Development

The mechanism of development of BRONJ is unclear. It is supposed that the disease results from suppression of bone metabolism after bisphosphonate treatment and from accumulation of physiologic micro-injuries of the jaw bones, compromising their biomechanical properties. Trauma and infection increase the need for bone recovery, which exceeds the capacity of hypodynamic bone, thus resulting in localized bone necrosis. Antiangiogenic properties of bisphosphonates and other medications taken by patients, as well as the presence of other comorbid factors, may promote the risk of development, persistence or progression of this condition.

Why Jaw Bones are Affected Most Often?

It is assumed that bisphosphonate-related osteonecrosis develops mainly in jaw bones because they, unlike other bones in the body, are not sufficiently protected. On one hand, an important fact is that they are protected from a possible intraoral trauma only by a thin mucous membrane and periosteum. On the other hand, the presence of teeth in the jaw bones allows easy penetration of microorganisms and development of intra-osseous infections - via the complications of dental caries and periodontal diseases.

Clinical presentation of intraoral lesions in BRONJ is zones of exposed yellow-white hard bone, with soft or indurated borders (Figure 1). Soft tissue lesions may be painful; they may merge with exposed bone and may affect extensive zones in the oral cavity [2]. In the initial stages, it is difficult to identify the boundaries between diseased and healthy bone visually (Figure 2). Often, the lesions are multiple and extra- or intra-oral fistulas may also be present (Figure 3).

Figure 1: Clinical presentation of bisphosphonate-related osteonecrosis of the mandible.

Figure 2: Surgically exposed mandible. Vital and non-vital bones have different colours, but the boundaries are rough and unclear.
In the advanced stages of the disease, sequestrations can form, which separate from the healthy bone spontaneously (in neglected cases), or this should be done surgically.

In the early stages of the disease, there may be no radiological changes. In view of early diagnosis, some authors recommend performing computed tomography. A method of choice is jaw bone scintigraphy with Tc-99m methylene diphosphonate. In advanced cases, the bone has a moth-eaten appearance, with clearly identifiable radiological features, with or without X-ray positive sequestration.

Findings in microbiological testing are aerobic and anaerobic microorganisms, and commonly actinomycte druses as well. Figure 4 shows colonies of microorganisms evidenced by fluorescent investigation. Histopathological analysis shows absence of a finding consistent with the disease treated with bisphosphonates, for example a malignant neoplasm metastasis, but presence of necrotic bone surrounded by bacteria, which do not invade it.

**Stages of Disease**

According to the American Association of Oral and Maxillofacial Surgery (AAOMS) [3], development of bisphosphonate-related osteonecrosis of the jaw occurs in four stages:

- **Stage zero (0)** - vague symptoms that may obscure the clinical picture, leading to delayed diagnosis.
- **Stage one** - bone exposure without any pain syndrome and signs of inflammation is observed.
- **Stage two** - bone exposure with pain syndrome and signs of inflammation is observed.
- **Stage three** - manifestation is characterized by bone exposure, pain and inflammation, and complications such as pathologic fracture, extraoral fistula, extension of the lesion to the base of the mandible and the floor of the maxillary sinus (AAOMS 2007, [4]).

To the third stage, we add also sequester formation (Figure 5) in the impaired area [5].

**Triggering Factors**

**Risk Factors Associated with Bisphosphonate Administration**

The risk is related to bisphosphonate administration. By literature data, the potential of development of osteonecrosis as a result of administration of amino-bisphosphonates (Zoledronate and Pamidronate) is greater than that of non-amino-bisphosphonates (Clodronate) [6,7]. Perhaps the most important factor for the occurrence of bisphosphonate-related osteonecrosis of the jaw is the duration of treatment [4, 8,9]. Badros et al. [10] suggested that the risk of developing bisphosphonate-related necrosis of the jaw was increased by 57% with each year after diagnosing multiple myeloma and starting its treatment.

Bamias A et al. [5] suggests that there is a strong correlation between the duration of bisphosphonate treatment and manifestation of jaw osteonecrosis. They found that the risk of developing this condition varies from 1% (12 months after the start of treatment) to 11% in the fourth year.

The authors reported that these figures vary depending on the type of bisphosphonate administered in patients treated with Zoledronic acid only from 1% in the first year to 21% in the third year since the beginning of the treatment, while in patients treated with Pamidronate with or without Zoledronic acid varies from 0% in the first two years of treatment to 7% after four years of treatment.

**Risk Factors Related To the Dento-Alveolar System**

This group of predisposing factors includes the presence of mandibular tori, palatal tori, and bone exostoses - sites in which local injuries can occur more easily as a result of jaw functions or of chronic trauma due to removable dentures. It is very important to precisely define the indications and contraindications for dento-alveolar surgical procedures - standard extractions, difficult extractions, extractions of impacted teeth, periodontal surgery, augmentation procedures and placement of implants.
This also includes the diseases of the hard dental tissues and tooth-supporting apparatus, caries and its complications, periapical changes in tooth roots, periodontitis and diseases of the oral mucosa.

The most common dental condition concomitant with BRONJ is periapical changes in teeth, which are clinically manifested or radiologically found in 84% of patients. Dental caries in necrotic zones was registered in 28.6%.

**Treatment**

Treatment of bisphosphonate-related osteonecrosis of the jaw is combined: conservative and surgical. The principles of conservative treatment are: systemic medication treatment with the triad: antibiotics, antifungal agents and antiviral agents. Particular attention should be paid to the response of the actinomycete druses which are the most common finding in microbiological tests. Clinical practice has proven that the combination of antibiotics and antifungal agents provides good results and the inflammation of the soft tissue around the bone lesions resolves within a period of seven to nine days.

Special attention should be paid to the local oral hygiene, which is to be maintained with chlorhexidine-containing agents.

With respect to surgical treatment, there is still controversy among researchers on the type of surgery and the time of performing it. One group of authors [11] recommend superficial curettage and prolonged conservative treatment. Another group of authors [12] recommend hyperbaric oxygenation, superficial debridement, laser treatment, and in advanced cases - aggressive resection of the diseased bone and soft tissue. Hoff, et al [13], reported healing process in 23% of the patients treated with conservative therapy only. Lazarovici et al. [14] reported healing process after superficial curettage in 82% of the cases. Some authors completely remove the diseased bone, covering the site with mucosa, and report good results in 85% to 100% of the patients [15,16]). Ferlito S et al. [9] reported that of 94 patients, in three of whom debridement was performed, and in 91 patients sequestrectomy was performed. Similar results were reported by another author [17], who identified the boundaries of the diseased bone using fluorescent light. This technology has been used in our practice for two years. The analysis of a number of publications shows that in the early stages of the disease (AAOMS 1 and 2) most authors administer medication therapy and conservative treatment, and in stage 3 resection and/or sequestrectomy are performed. The method proposed by Otto S et al. [17], reported by Assaf AT et al. [18], uses fluorescent light for visualization of vital and non-vital bone, is a new and promising method for demarcation when performing resection of the jaw (Figure 6).

**Prevention**

Before the start of bisphosphonate treatment, full oral cavity sanitation needs to be performed, and this is one of the major factors for preventing the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ). That is why oncologists administering this type of therapy have to be familiar with the dental aspects of this debilitating complication and the need for dental prophylaxis.

One month prior to initiation of bisphosphonate treatment, the following dental procedures may be carried out: standard extraction of teeth refractory to conservative treatment, periodontal surgery, endodontic treatment, removal of tori covered with very thin and delicate mucosa, extraction of partially impacted teeth, treatment of caries, prosthetic restorations. In terms of impacted teeth, only those which are not fully covered by bone are to be extracted.

Experience in dental treatment during and after bisphosphonate therapy is based on avoiding, if possible, invasive procedures, and if it is not possible, drug protection must be administered. Surgical procedures should be minimally invasive and minimally traumatic and should be carried out by specialists in oral or orofacial surgery.

**Discussion**

The mechanism of development and progression of BRONJ is still unclear. As some authors argue (Allen MR and Burr DB [19], there are many hypotheses, but still pathophysiologists cannot answer to the question:- What is the intimate mechanism of development of BRONJ?

We can assume that the clinical course is clear, especially since publishing "Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws" (American Association of Oral and Maxillofacial Surgeons) in 2007 in which the disease was divided into stages with precise clinical characteristics.

Numerous publications clarified in detail the most important factors for the development of BRONJ, which are rightly categorized as: factors associated with bisphosphonate administration and dento-alveolar factors.

Many different opinions on the triggering factors may be found in literature, but the most widespread view is that these are primarily traumas of dentoalveolar system and curative dental procedures. In this particular part of the challenge BRONJ, it is necessary to establish a precise operative protocol for dental treatment of patients taking bisphosphonates or having clinically manifested development of osteonecrosis.

Principles of medication treatment have been clarified and there is a consensus among specialists. With respect to surgery, I think that more and more surgeons come to the conclusion that non-vital bone must be removed by bone resection. Difficulties in early resection are due to the fact that the boundaries between vital and non-vital bone are difficult to identify. Interesting results were reported with the use of fluorescence diagnostics, contributing to precise demarcation of boundaries.

In conclusion, we can say that in order to reduce the number of cases of BRONJ, full prevention in patients who are going to receive bisphosphonate treatment must be carried out, but this is a huge amount of work and is a challenge for the dental community.
References


