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OBSERVATIONAL STUDY OF THE BISPHOSPHONATE-RELATED OSTEONECROSIS OF JAWS

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Abstract

Introduction. *The bisphosphonate-related osteonecrosis of the jaw was first referred to in 2003. Bisphosphonates action is focused on the osteoclasts. The drastic inhibition of the osteoclastic function is harmful for the jaws which are the only bones of the human skeleton in relative contact with the external environment. The adverse effects of the bisphosphonate-related therapy include the pathology for which they are prescribed, the atypical fractures in pathological bone.*

Method. *The aim of this research was to analyze the risk factors and the treatment methods in case of osteonecrosis of the jaws. To achieve these goals, the author analyzed the observation sheets of the patients admitted to the Oral and Maxillofacial Surgery Clinic during the period 2010-2015. The inclusion criteria were as follows: treatment with bisphosphonates, current or previous; the lesions of the mucous gingiva of the maxillaries followed by exposed necrotic bone, older than 8 weeks, with no tendency of healing; specific radiological image showing extended osteolysis with diffuse outline or radiopacity surrounded by radio-transparence, representing the necrotic bone sequestered; no metastasis in the necrotic maxillary bone; patient with no medical background of cervical-facial radiations. The patients who met these criteria were admitted in the study after signing the informed consent. Afterwards, the information found in the notes of the observational sheet (anamnesis, general examination and the imagistic investigation, treatment, postoperative recovery, prescription, postoperative recommendations) were gathered and submitted for statistic analysis*

Results. *Of the 20 patients in total, 13 were women and 7 men, of ages ranging from 43 to 83. The most numerous cases were registered in the seventh age decade. All patients included in the study had lesions of the gingival maxillary mucosal areas with exposure of the subjacent necrotic bone. 60% of them were under intravenous treatment with zoledronic acid (Zometa®). A single patient was under oral treatment with bisphosphonates. 19 of these 20 patients developed osteonecrosis following a dental extraction while one case was due to the instability of the mandibular mobile*

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prosthesis. 61% of the patients included in the study developed a necrotic process in the mandibular bone, 80% of the localizations were in the posterior area. As first intention, the choice of treatment was represented by local lavages with antiseptic solutions, general antibiotics and sequestrectomy. Of these patients, a third had relapsed and needed radical surgery treatment.

Conclusions. *Prevention of the bisphosphonate-related osteonecrosis of the jaw represents the best method of treatment. The development of bone sequesters damages the volume of the maxillary bone as such, reducing the chances for prosthetic functional rehabilitation of the dento-maxillary system. An increase in the quality of life by oral restoration of these patients may represent a challenge.*

Keywords: bisphosphonate-related osteonecrosis of the jaw, pathologic bone fracture, osteoclast, osteonecrosis, osteoporosis

Background and aim

Bisphosphonates represent the most prescribed therapy against osteoporotic pathology. However, this medicine is often found in the therapeutic regimes meant to prevent and to treat bone metastasis of different types of cancer such as breast, prostate or multiple myeloma [1]. Due to the incapacity of being metabolized, they accumulate in the bone and therefore favor complications such as osteonecrosis of the jaws. New research has concluded that other inhibitors of the osteoclastic function (denosumab, bevacizumab) may determine osteonecrosis of the jaws under conditions of bone trauma. Both bisphosphonates and monoclonal antibodies have a therapeutic effect focused on reducing the function of osteoclasts. Uncontrolled inhibition, with the reach of a critical threshold of over 50% of the total cell mass, may represent the start of the osteonecrosis [2].

In the malignant pathology, bisphosphonates reduce the progression of the bone metastasis, maintain calcium blood levels within normal limits and reduce the symptomatology and complications that occurred in the bone manifestation of cancer (bone pains, pathological fractures). In general, bisphosphonates come to complete the basic therapy such as chemo- or radio therapy, whereas the main route of administration is intravenous. This route is preferred especially for treatment of bone metastasis. Due to intravenous administration, bisphosphonates reach the cellular level rapidly and reduce the population of osteoclasts before they respond to the activating signal transmitted by the tumoral cells [3,4].

Recent studies have shown the synergic effect of associating dexamethasone and bisphosphonates in reducing the speed of tumoral growth. Bisphosphonates are mainly used in the osteoporosis therapy. Their therapeutic effect diminishes the risk of pathologic fractures of the hip, radius and vertebras. The dosage and the duration of the treatment are established in line with the stage of the disease and the patient's age.

The bisphosphonates therapy may determine numerous side effects, of which we mention some of the most frequent.

By inhibition of the bone resorption, bisphosphonates may determine a transitory hypercalcemia, which leads to the depletion of the bone calcium and the increase in the level of the parathyroid hormone (PTH), whose role is to adjust the calcium-phosphorus ratio in bones and kidneys [3,4,5].

In very few cases bone fractures (tibia, hip bones, vertebras) were reported. Their causes were established to have been an extreme inhibition of the bone remodeling. 6% of the patients treated with bisphosphonates had generalized bone pains, myalgia, arthralgia [4]. These same patients suffered gastrointestinal intolerance associated or not with esophagus lesions. The patients treated with intravenous bisphosphonates had painful symptomatology in the bones, muscles, joints, headaches, nausea and vomits, dizziness, fever. These symptoms occurred on the day of drug administration and lasted 3 to 4 days. Side effects were also seen in the ocular area (uveitis, conjunctivitis) and kidneys.

In the oral cavity, side effects of the therapy with bisphosphonates may be more or less serious. The therapy with bisphosphonates may cause oral ulcerations due to digestive adverse effects caused by medication (nausea, vomits). The etidronate alters the primary immune response and determines exacerbation of the viral herpetic infections and other ordinary viruses.

The major complication of this treatment is the Bisphosphonates-related osteochemonecrosis of the maxillary bones which represents the exteriorization of the necrotic bone sequestered in the healthy bone, followed by the development mucosal lesion oral cavity under the form of at least eight-week lesion, without healing tendency [6,7,8].

In February 2009, the first BRONJ classification was introduced. Depending on the parameters of the bisphosphonates treatment, the patients may be classified into two categories:

1.Patients exposed to risk (previous treatment with bisphosphonates) yet without necrotic bone lesions or typical symptomatology.

2.Patients with visible pathology.

Once intraoral lesions occur, BRONJ undergoes 3 clinical evolution stages for which treatment encompasses several lines of action:

1.Necrotic bone exposed, without painful symptomatology. For these patients, minimal conservative treatment may be applied, as it has proven to be efficient in the disease worsening prevention, followed by lavages with antiseptic solutions (chlorhexidine 0.12%)

2.Necrotic bone exposed, with pains and infection. To fight infections, in addition to lavages with antiseptic solutions, an antibiotic will be administered, usually from the penicillin group. In order to exclude an infection with actinomycotic species an antibiogram will be required.

3.Necrotic bone exposed, with pain, infection, pathological fracture, extraoral fistulas, signs which indicate extension of the osteolysis process to the opposite cortical side. Due to the extended damage of the bone support, the main therapeutic direction aims to remove the necrotic tissue and to continue healing the neighboring tissues [1,4,9,10].

The latest census on the prevalence of the bisphosphonates-related osteonecrosis of the jaws was completed in 2003. The study was undertaken in two centers of Maxillofacial Surgery in San Francisco [11] and in Miami [12]. The results of the research were published in the Journal of Oral and Maxillofacial Surgery and concluded that the osteonecrosis of the jaw has a prevalence ranging from 1 to 10% of the cases treated with intravenous bisphosphonates and only 0.001 to 0.1% of the cases with oral bisphosphonates [7].

The aim of this study is to analyze the efficiency of the usual therapy applied in osteonecrosis of the jaws and the possibility to improve the quality of life after treatment.

Material and method

The authors have undertaken a retrospective study which included patients hospitalized in the Oral and Maxillofacial Surgery Clinic II in Cluj-Napoca, between January 2010 and June 2015, patients who met the criteria of inclusion in the study:

• Treatment with bisphosphonates, current or previous.

• The lesions of the mucous gingiva of the maxillaries followed by exposed necrotic bone, older than 8 weeks, with no tendency of healing.

• Specific radiological image showing extended osteolysis with diffuse outline or radio-opacity surrounded by radio-transparence, representing the necrotic bone sequestered.

• No metastasis in the necrotic maxillary bone.

• Patient with no medical background of cervical-facial radiations.

In order to obtain a confident diagnosis, the researcher analyzed the medical charts of the patients admitted to the study and obtained data from the clinical and radiological examination. Specific modifications of osteonecrosis were revealed.

For data collection, the medical charts of the patients diagnosed with bisphosphonates-related osteonecrosis or osteomyelitis were studied. After thorough investigation 20 cases fulfilled the criteria of inclusion in the study.

All patients included in the study had lesions of the gingival mucosa of the jaws with exposure of the subjacent necrotic bone associated with great pain, radiating from the active lesion. According to the signs and symptoms found at the first examination, none of the patients included in this study were diagnosed in stage 0 or 1 of the disease. The first choice of treatment was represented by sequestrectomy and lavages with local antiseptic solutions and general antibiotics. Of these patients, a third had relapsed and needed radical surgery treatment.

Data were gathered from general clinical examination and imaging (Cone Beam Computer Tomography), and later arranged in 3 groups:

1.Personal pathological antecedents, of which the following were considered of major importance: reason to go the specialty ward, pathology for which bisphosphonates treatment was prescribed, type of bisphosphonate administered, route of administration, causal factor of osteonecrosis, timeframe between the occurrence of the causal event and the osteonecrosis, associated treatment, which influenced the evolution of the osteonecrosis.

2.General and radiological examination focused on highlighting the changes specific to osteonecrosis: localization of osteonecrosis – in the maxillary, in the mandible or in the bimaxillary, hind or fore.

3.Data on the treatment with bisphosphonates:

a. Disruption in treatment, noncompliant patient,

b.Observance of treatment as prescribed, compliant patient,

c. Completion of treatment.

Results

Of all patients, 13 were women and 7 men, of ages ranging from 43 to 83, the most numerous cases being registered for the seventh decade of age.

The main reason for going to the maxillofacial surgery department was pain associated with eating disorders (85%).

Figure 1 shows the distribution of jaw osteonecrosis cases depending on the pathology for which the patient was under a treatment with bisphosphonates. The highest percentage is represented by female patients suffering from mammary carcinoma, followed by male patients suffering from prostate carcinoma.

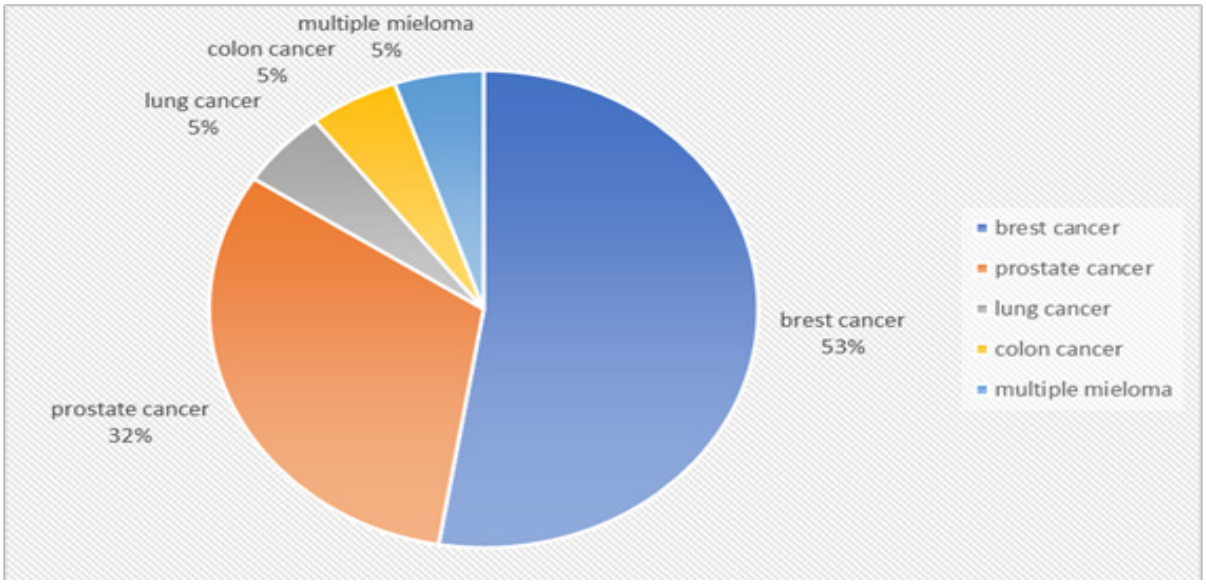

Figure 1. The distribution of the cases depending on the pathology for which bisphosphonates were administered.

Most patients who suffered from osteonecrosis of the jaw were previously under treatment with Zolentronate traded under the name of Zometa® - 60%. The zoledronic acid is an intravenously administered amino- bisphosphonate with the highest relative potency in this pharmacological group (10,000 times as high as etidronate). Consequently, this bisphosphonate is most frequently associated with osteonecrosis of the jaws.

Bondronat®, or by its pharmacological name Ibandronate, is responsible for causing 30% of the jaw osteonecrosis cases. The 10 minority percentages are represented by patients who were administered Alendronat (Fosamax®) and other oral bisphosphonates. These findings indicate that orally-administered bisphosphonates have been the least frequently associated with the pathogenesis of the jaw osteonecrosis.

Of the 20 patients admitted in the study, only one was administered oral bisphosphonates.

Causal Factors of BRONJ

Most patients who met the criteria to be included in the study developed osteonecrosis following a dental extraction. Only one case of the 20 was due to the instability of the total prosthesis. In addition to the factor above mentioned, incriminated in the occurrence of the osteonecrosis are also malnutrition, excessive smoking, abuse of alcohol and immunosuppression therapy. Corticotherapy takes a special place among the triggers, due to the action mechanism on the primary immune system and the osteoclasts. Therefore, extended corticotherapy causes osteoporosis of which treatment is represented by bisphosphonates. The risk to develop osteonecrosis of the jaws is even higher when the immune response is poor. This class of patients require interdisciplinary examination and well-analyzed therapeutic conduct.

Localization of the Osteonecrosis Process

Regarding the prevalence of the localization of the osteonecrosis process in one of the two maxillary bones, there has been found that there is an affinity of this pathology for the mandibular bone, fact also explained by the metabolism differences between the two bones compared.

In addition, a high prevalence was found in case of hind localizations of the necrotic process, as indicated in figure 2.

The choice treatment in the patients admitted in the study was sequestrectomy, as most of the patients included in the study presented signs and symptoms of BRONJ stage 3. Few patients had different degrees of relapse after weak antiseptic lavages. No patient admitted in the study received radical resection treatment of a bone compartment, as shown in figure 3.

Most commonly, patients admitted to the study received amoxicillin with clavulanic acid (Augmentin®), 30% received Cefuroxime, 20% clindamycin and only 10% ciprofloxacin.

Treatment Applied in First and Second Hospitalization

Of the 7 patients who returned to hospital due to relapses, 6 underwent sequestrectomy and only one patient was administered antiseptic lavages.

Upon the second hospitalization, in one patient a dental unit was extracted, followed by sequestrectomy, and another patient underwent a hemi mandibular resection, as shown in table I.

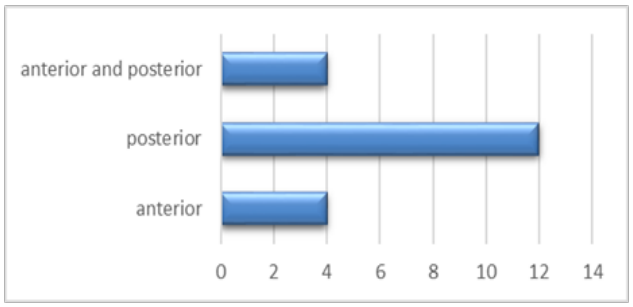

Figure 2. Distribution of patients depending on the localization of the necrotic process.

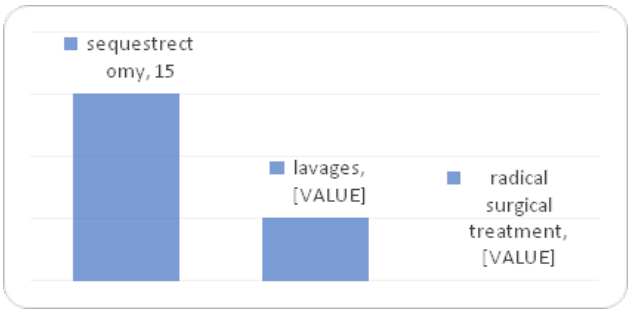

Figure 3. Distribution of patients depending on the treatment applied.

Table I. Types of treatment applied to patients who had relapses.

	First hospitalization	Second hospitalization
Patient 1	sequestrectomy	extraction
Patient 2	sequestrectomy	hemi mandibular resection
Patient 3	sequestrectomy	sequestrectomy
Patient 4	sequestrectomy	sequestrectomy
Patient 5	sequestrectomy	antiseptic lavages
Patient 6	sequestrectomy	sequestrectomy
Patient 7	sequestrectomy	sequestrectomy

Discussion

This study aimed to analyze the clinical characteristics and the treatment of bisphosphonates-related osteonecrosis of the jaws. The results obtained were compared to results in previous studies [7,13]. The common parameters which can be found both in the studies cited and in this study, are represented by demographic data, the patient's personal pathological antecedents, as well as the antecedents relating to the pathology for which bisphosphonates were prescribed, pathological intraoral and extra-oral elements, medication during hospitalization, relapses [4,7].

With regards to demographical data, previous studies [14] highlight a major frequency of diseases among women (61%), similar to what we showed in this study (65%). A meta-analysis conducted in 2015 concludes that most studies published between 2010 and 2014 indicated the same ratio of 2:1 between the female and the male cases [15].

In most cases the age (70-74) matches the age indicated in other studies where patients around 68 years old [8].

Similar to this study, Woo's study [16] finds a time interval of 1 to 3 months between occurance of the risk event (dental extraction, lesions due to an unstable prosthesis) and the patient's presence in the specialty ward, due to painful symptomatology. Medical literature has often shown the interval of 4 to 6 months from the triggering event until occurrence of symptomatology. A retrospective study conducted in 2015 on a group of 72 patients in Munich finds a similar time interval between the triggering event and the osteonecrosis. Additionally, the author pinpoints the multitude of risk factors influencing the healing of the post-extraction wound (poor local hygiene, abuse of toxic substances, tobacco, alcohol, bacterial infections) and states that the dental extraction surgery does not represent a dominant factor of osteonecrosis but rather the local post-surgery conditions which may alter the healing process [9]. A study conducted in China on female patients suffering from mammary cancer with bone metastasis, under treatment with zoledronic acid, indicated an average of 8.58 months between the dental extraction and the occurrence of osteonecrosis [6].

The decision as to the best moment when to invasively intervene in the area of the maxillary bones represents the first positive undertaking in the prevention of the osteonecrosis of jaw. Located in the bone, the bisphosphonates have a halving time of 10 years, timeframe in which the risk of osteonecrosis persists. A relative indicator of the confidence as to bone regeneration and resumption of the osteoclastic function is the CTX dosage (c-terminal telopeptide) in the peripheral blood. The normal CTX value in blood is 350-500 pg./ml and is the result of the degradation of type I collagen in the bone caused by the osteoclasts. During the bisphosphonates treatment, it drops dramatically down to values of 30-60 pg./ml as a result of osteoclastic hypo-function. After a 9-month of bisphosphonates treatment disruption, CTX goes up to 150 pg./ml. These are values suitable for safe interventions on the bone tissue as the osteoclastic function is restored at reasonable quotas [8]. This study does not include this

test since it becomes groundless after osteonecrosis has occurred.

The majority - 97% of patients have received the intravenous treatment and only 3% the oral administration. Similar results are found in Filleul's study, with 88% of the patients under intravenous administration and 12% P.O. [14].

The only bones of the human skeleton which relatively relate to the exterior are the maxillary bones. They communicate with the oral cavity through the periodontal space. This condition increases the susceptibility to bone infections. The terminal type circulation and the anti-angiogenetic effect of bisphosphonates explain the predisposition of maxillary bone to osteonecrosis, especially the mandible. This study has found a 55% prevalence of the mandible affectation, similar to the ones in Filleul's study (65%) and Beniatti's study (mandible-maxillary affectation ratio 2:1) [14,15].

Ninety-five percent of maxillary osteonecrosis cases were the results of a dental extraction and only one case was due to decubitus lesions caused by unstable total prosthesis. The studies focused on the discovery of osteonecrosis factors have shown the synergy between the microenvironment neighboring the healing bone and the general factors such as corticotherapy [8].

In initial treatment, the osteonecrotic lesions were sequestrated (75%), only 25% of them requiring antiseptic lavages. This finding is explained by the lack of primary stages patients included in the study, since their lesions do not require hospitalization. Similar percentages were discovered in other studies in medical literature [17]. A recent study focused on methods to treat stage I and II osteonecroses encourages minimally invasive surgery interventions, muco-periosteal detachment not being required to close the bone defect; on the contrary, use of hemostatic bandages is encouraged to support per secundam healing [18,19].

As for the medication associated with surgical intervention, in this study amoxicillin with clavulanic acid had the prevalence (40%), similar to the therapy applied in Filleul's study where ampicillin was administered in 39% of cases.

Conclusions

Since 2003 the medical world has been facing up to the aberrant increase in the number of bisphosphonates-related jaw osteonecrosis cases. The practitioners of that time focused in their researches on finding alternative minimum adverse-effect therapies and on introduction of complete prevention and treatment protocols.

The prevention of bisphosphonates-related jaw osteonecrosis represents the best management strategy. Development of sequestra damages the volume of maxillary bones and reduces the possibilities for prosthesis and the rehabilitation of the stomatognate system functions. The increase in the quality of life by oral rehabilitation of these patients may represent a challenge.

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