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Bisphosphonates-induced osteonecrosis of the jaw – epidemiological, clinical and histopathological aspects

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Abstract

Introduction: Osteonecrosis of the jaw (ONJ) is a multifactorial condition associated with bisphosphonates (BPs) treatment, head and neck irradiation, malignancy, chemotherapy, periodontal disease or trauma. The first cases of BPs-related ONJ (BRONJ) were reported over a decade ago. *Patients, Materials and Methods*: The study was retrospective and analyzed archived material. The study included 38 patients diagnosed and treated in the Clinic of Oral and Maxillofacial Surgery, Emergency City Hospital, Timişoara, Romania, for BRONJ, between 2013 and 2016. For all the cases were noted gender, age, localization of osteonecrosis, therapeutic indications for BPs (osteoporosis or malignancy), history of radiotherapy or chemotherapy, presence of bone metastases. If the treatment consisted in surgical removal of necrotic bone, the surgically removed specimens were sent to Service of Pathology of the same Hospital. The excised specimens were prepared with routine histological technique. *Results*: All the patients included in the current study were diagnosed with BRONJ. The patient history and clinical characteristics were the most useful diagnostic methods. Radiographic changes are not significant in early stages of osteonecrosis. The prevalence of BPs-associated ONJ is higher between 55–74 years old. *Conclusions*: ONJ is an important complication of BPs medication. The majority of affected patients develop this complication after dentoalveorar surgery, especially after dental extraction. Therefore, a good state of dental health is one of the most important directives when dealing with potential candidates for BPs therapy.

Keywords: osteoporosis, osteonecrosis of the jaw, bisphosphonates.

Introduction

Osteoporosis is an age-related condition being, in elderly people, an important cause of orthopedic trauma. The commonly involved bones are vertebra, hips and forearms. Frequently, there are no symptoms on the site before the bone breaks down.

One of the most common medication used to prevent osteoporotic fracture are bisphosphonates (BPs), anti-resorptive medication that can be administrated oral or intravenous [1–4].

Osteonecrosis of the jaw (ONJ) is a multifactorial condition that can be frequently linked with antiresorptive and antiangiogenic therapies used to treat both, different malignancies, and osteoporosis. Other causes of ONJ included periodontal disease and trauma.

Over a decade ago, first cases of BPs-related osteo-necrosis of the jaw (BRONJ) were reported in association with this medication.

In 2014, the updated recommend of *Special Committee* appointed by the *American Association of Oral and Maxillofacial Surgeons* to change the nomenclature of BRONJ to nomenclature to medication-related osteonecrosis of the jaw (MRONJ) was well received because lately many other antiresorptive [receptor activator of nuclear factor-*kappa* B ligand (*RANKL*) inhibitors] and anti-angiogenic therapies besides BPs was considered in the treatment of the osteonecrosis cases [5–8].

The risk factors for MRONJ are classified as medication-related risk factors, local factors, demographic and systemic factors and other medication factors, genetic factors [9–16].

Regarding the medication-related factors, two elements were noted: therapeutic indications (osteoporosis or malignancy) and type of medication (BPs and non-BPs).

Zoledronate is an intravenous BP that inhibit osteoclast activity, being used to treat different conditions as osteo-porosis, high blood calcium and bone breakdown due to cancer and Paget's disease of bone.

Denosumab, a monoclonal antibody, is a *RANKL* inhibitor from the category of non-BPs medication used to treat different conditions that involve bone loss (osteo-porosis or medication complication), or bone replacement by primary tumor or metastases, because it prevent osteoclast development [8].

The objective of the study was to assess the epidemiological, etiological and histopathological aspects of BRONJ.

Patients, Materials and Methods

The study was retrospective and analyzed archived material. Between January 2013 and December 2016, 40 patients were diagnosed and treated in the Clinic of

Oral and Maxillofacial Surgery, Emergency City Hospital, Timişoara, Romania, for BRONJ.

Criteria for inclusion in the study

All the patients included in the current study were diagnosed with BRONJ. Patients may be considered to have BRONJ (or MRONJ) if all of the following characteristics are present: (*i*) current or previous treatment with antiresorptive or antiangiogenic agents; (*ii*) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks; (*iii*) no history of radiation therapy to the jaws or obvious metastatic disease of the jaws.

Because two cases performed radiotherapy in the head and neck area, these cases were excluded from the study; therefore, the final patients' group included 38 cases. For all the cases were noted gender, age, localization of osteonecrosis, therapeutic indications for BP (osteoporosis or malignancy), history of radiotherapy or chemotherapy, presence of bone metastases.

The statistical analysis was performed with Microsoft Excel and Statistical Package for the Social Sciences (SPSS) ver. 17.0. Descriptive statistics for numeric variables were done. Mann–Whitney test and χ^2 (chi-square) test were used for comparing data.

If the treatment consisted in surgical removal of necrotic bone, the specimens were fixed in 10% (*v/v*) buffered formalin and sent to the Service of Pathology of the same Hospital, being processed using the routine histological technique in order to obtain paraffin blocks.

For all cases, 3 μm thick sections were cut on a Leica RM2245 semi-automated rotary microtome and mounted on histological slides. For morphological diagnosis, the slides were stained with Hematoxylin–Eosin (HE). In order to highlight the bacterial flora, Periodic Acid–Schiff (PAS) reaction was used.

Histopathological evaluation was performed with Leica DM750 microscope. Images were acquired using Leica DM Share system.

The local Ethics Committee approved this study, and written informed consent was obtained from all the patients.

Results

The majority of patients were females, only 18% being males. The patients were between 47 and 81 years old (average: 64.98 years, standard deviation: 8.056, variance: 64.902).

Twenty-nine (76%) of the patients were treated with BPs for osteolytic bone injury and nine (24%) for osteoporosis prophylaxis. We noted that 24 (63%) patients with osteolytic lesions had metastases. Therefore, nine (24%) patients had bone metastasis from the prostate adenocarcinoma, eight (21%) patients from the ductal breast carcinoma, four (11%) patients from the renal clear cell carcinoma, two (5%) patients from the colon adenocarcinoma and one patient (2.6%) from the lung adenocarcinoma. Out of 29 patients with osteolytic lesions, four (11%) were diagnosed with multiple myeloma and one case (2.6%) with synchronous soft osteosarcoma of the chest wall and renal cell carcinoma.

The therapeutic indication for BP was osteoporosis – seven (18.42%) cases and malignancy – 31 (81.57%) cases. The number of females with osteoporosis was significant higher than males (χ^2 test, p=0.006, α=0.01). Four (9.52%) patients had history of radiotherapy and six (14.29%) patients had history of chemotherapy. Thirteen (30.95%) patients presented bone metastases. There were no significant differences between the presence/absence of bone metastases and gender (χ^2 test, p=0.588) and age groups (χ^2 test, p=0.772).

The χ^2 concordance test was used to determine if there are significant associations between occurrence of osteonecrosis in neoplastic pathology and osteoporosis and we found a value of p=0.15 (α=0.05, 5%).

Ten (26.3%) patients received oral BPs (Boniva or Fosamax) and 28 (73.7%) patients received intravenous BPs (Zometa or Pamired). The Spearman's correlation coefficient for the patients treated with oral BPs was 0.05. In contrast, patients treated with intravenous BPs, have the Spearman's correlation coefficient 0.28.

Thus, 27 (71%) patients with ONJ were treated with Zometa (4 mg zoledronic acid solution), intravenous solution, one per month; six (16%) patients with Boniva (150 mg ibandronic acid tablets), oral administration, one per month; four (11%) patients were treated with Fosamax (70 mg alendronic acid tablets), oral administration, one per month. One patient (2.6%) was treated with Pamired (90 mg/250 mL disodium pamidronate solution) one per month.

The six patients treated with Boniva had a period between one year and 10 years, with an average of 40 months, from the initiation of the treatment to the occurrence of the osteonecrosis. Treated with Zometa, they presented symptoms of osteomyelitis in a period between three months and three years, with an average of 32.11 months.

It was established that five patients have recently a dental extraction and one gingival infection (abscess of right canine fossa). At the rest of 32 patients, osteonecrosis was apparently spontaneous, without noticing an obvious factor. Still, among these patients, one patient is chronic smoking, three patients associate type II diabetes, three are seen with rheumatoid arthritis, one has recently presented septic status with suppurative peritonitis and five patients have followed chemotherapy treatments for primary malignancy. Out of those five, one concurrently associates cures of chemotherapy and radiotherapy for colon cancer. There were also identified four patients who received radiotherapy for prostate (one patient) and breast cancer (three patients), but not in the head and neck region, which is why they were included in the examined group.

Thirty-one patients presented osteonecrosis in the mandible, majority with unilateral localization (30 patients) and one with bilateral localization. Six patients presented maxillary localization – four in the right side and two in the left side. One patient had concomitant mandibular and maxillary affection. We found a mandibular/maxillary involvement ratio of 5:1. There were no significant differences between localization of osteonecrosis and gender (χ^2 test, p=0.134) or age groups (χ^2 test, p=0.725).

All patients had the following signs and symptoms: pain in the jaw area, exposed yellow-white bone with

sequestration, tooth mobility, abundant purulent discharge, erythema, ulceration, fistula, suppuration and gingival infection (Figure 1).

Moreover, edentulous regions also exposed bone (Figure 2). History of local trauma was not a sine qua non condition to expose bone. If infection of necrotic jawbone appeared, intraoral and extraoral fistula were noted (Figure 3).

A panoramic radiography was performed on all patients with clinical suspicion of maxillary osteonecrosis. This reveals the following: bone sequestration surrounded by a radiolucent area, radiopaque sinus, osteolysis, empyema and hypertrophic mucosa (Figure 4).

Radiographic changes on orthopantomogram (OPG) or retro-alveolar radiographs are not significant in early stages of osteonecrosis until there is significant bone involvement or demineralization. On radiographic images, an early sign of osteonecrosis could be represented by the lack of extraction site ossification (Figure 5). In late stages with extensive bone involvement, mottled bone or sequestrum appears. Cone-beam computed tomography (CBCT) can highlight a three-dimensional (3D) image of necrosis area, but has not proved to be useful with early diagnosis (Figure 6). CBCT was useful for planning surgical debridement procedures.

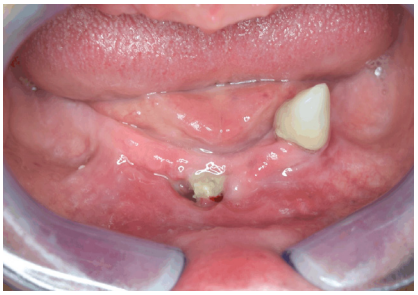

Figure 1 – ***Area of exposed necrotic bone in the anterior mandible surrounded by inflamed erythematous gingiva.***

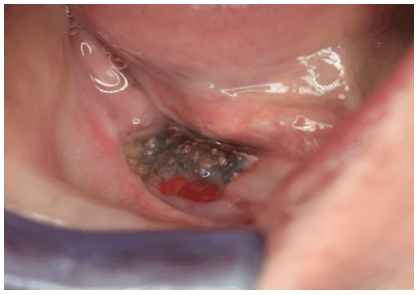

Figure 2 – ***Exposed necrotic bone in edentulous right mandibular area.***

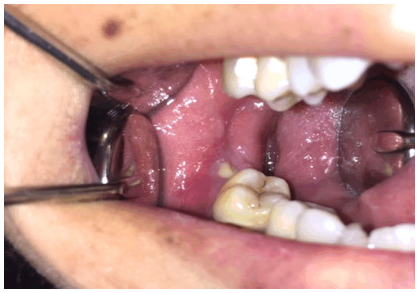

Figure 3 – ***Posterior right mandibular mucosal fistula in a dental extraction site that appeared in a patient with a history of Zometa (zoledronate).***

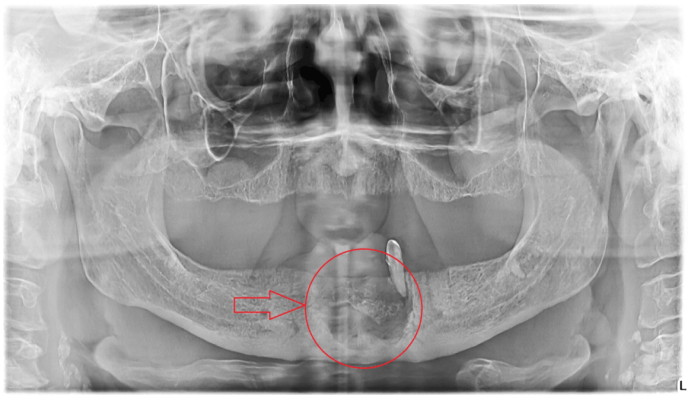

Figure 4 – ***Radiographic exam (OPG) shows a region of mottled bone with a central sequestrum in the left (L) anterior mandible. OPG: Orthopantomogram.***

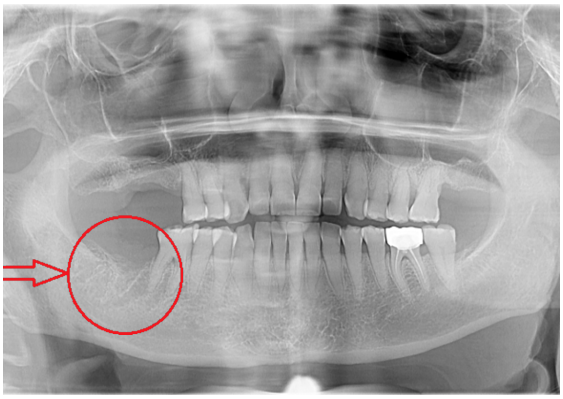

Figure 5 – ***OPG showing little ossification at a previous right mandibular extraction site. OPG: Orthopantomogram.***

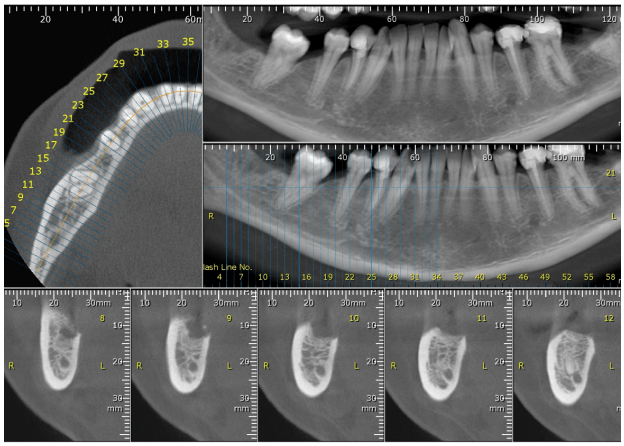

Figure 6 – ***CBCT 3D images showing little ossification at a previous right mandibular extraction site. CBCT: Cone-beam computed tomography; 3D: Three-dimensional.***

In all of the cases with osteonecrosis clinical suspicion, biopsy fragments were taken and a histopathology exam was performed.

HE staining was used for histological examination by light microscopy. The histopathological examination showed in all cases necrotic lamellar bone fragments, acute and chronic inflammation with lymphocytes, plasma cells, macrophages and granulocyte neutrophils, bacterial colonies, frequently with *Actinomyces* (PAS+) and epithelial denudation (Figures 7–9).

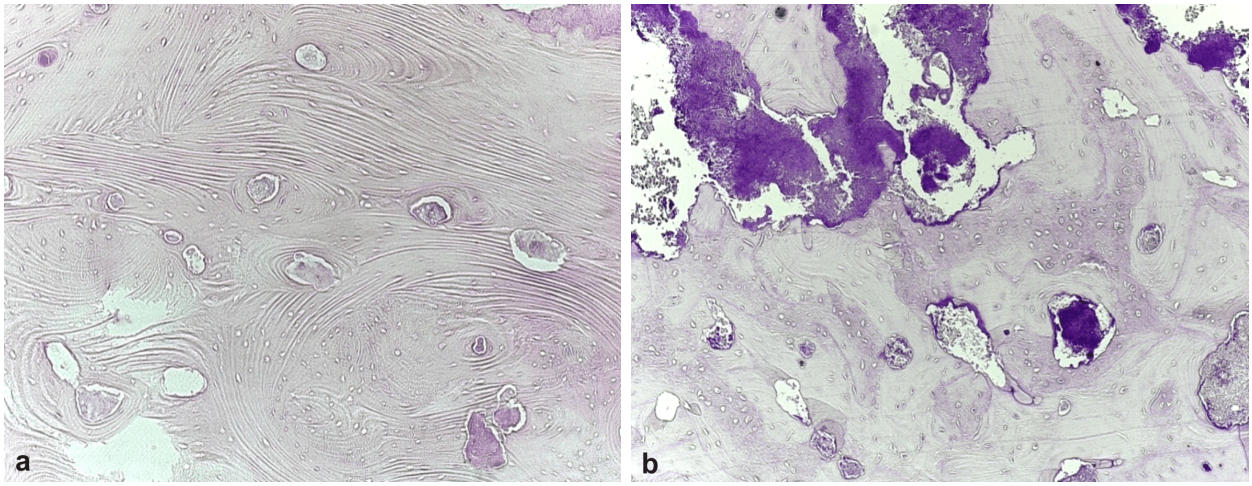

Figure 7 – ***(a) Light eosinophilic necrotic lamellar bone and small areas of cementification (HE staining, ×100); (b) Bacterial colonies at the periphery of necrotic bone (PAS staining, ×100).***

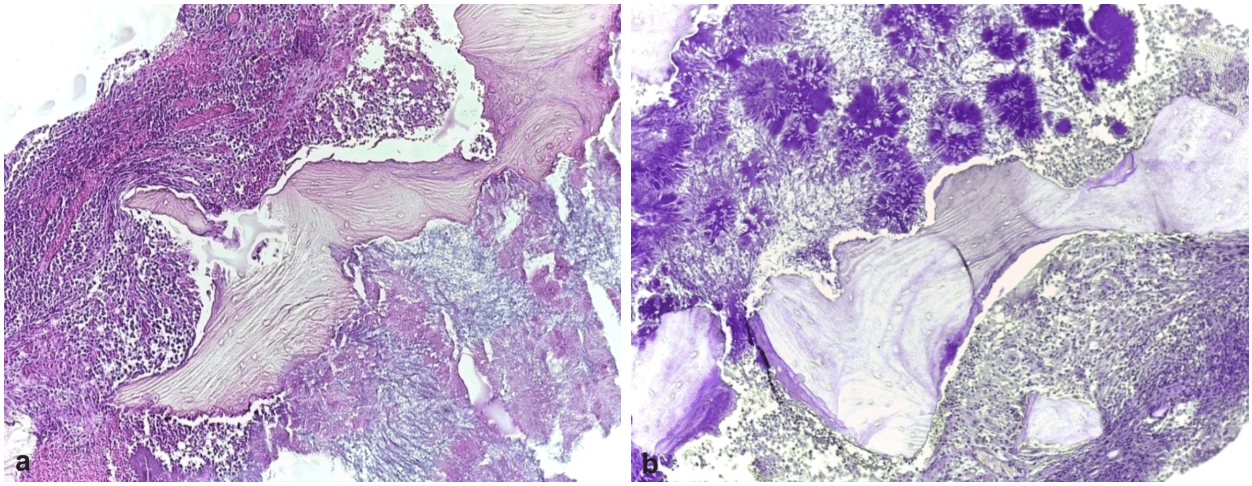

Figure 8 – ***(a) Osteonecrosis with areas of cementification and with massive inflammation (HE staining, ×100); (b) Lamellar necrotic bone surrounded by inflammation and bacterial colonies (PAS staining, ×100).***

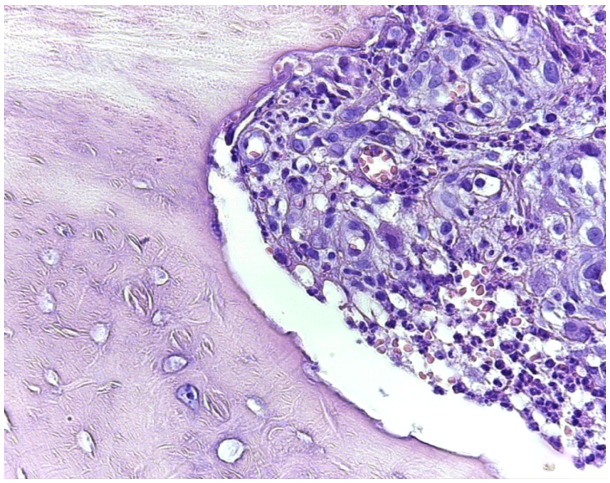

Figure 9 – ***Necrotic lamellar bone with osteoblasts riming and granulation tissue (HE staining, ×400).***

Discussions

Usually, in elderly people, the osteoporotic bones are so weaken that the break down appears after a minor stress or spontaneously. White and Asian population have a greater risk to be affected by osteoporosis. The condition is noted in elderly people, the incidence increasing from 15% of affected white people in fifth decade to 70% in seventh decade. Women are more commonly affected than men are. The most common risk factor for osteoporosis are advanced age, but different medications, whose use usually cannot be avoided, that can produce osteoporosis [1–4].

The osteoporosis appearance is due to an imbalance between osteoblasts bone formation and osteoclast bone resorption. Many molecules interfere with osteoclasts activation, *RANKL* is being the most studied. *RANKL* is produced by osteoblasts and stimulates *RANK*. The process

activates the osteoclasts. Osteoprotegerin, an important inhibitor of osteoclast genesis, is a competitor of *RANK* in binding process to *RANKL* and therefore inhibits the increasing of bone resorption [3].

Oral BPs are commonly used for osteoporosis and osteopenia, while intravenous BPs are used also to manage cancer related conditions especially bone metastases of a breast, lung or prostate primary solid tumor, or lytic lesions developed in patients with multiple myeloma [5–8].

The pathophysiology of MRONJ is a source of great debate and has not been fully elucidated [9–18]. Possible hypotheses include the inhibition of osteoclastic bone resorption and remodeling, or of angiogenesis and local repeated microtrauma. The other factors include suppression of humoral and cell mediated immunity, shortcoming of vitamin D, and soft tissue BPs toxicity. In addition, inflammation and infection is considered an important component of MRONJ [19–26].

The probability of MRONJ appearance among zoledronate-treated cancer patients is 50–100 times higher than for those not exposed to antiresorptive medications.

The risk for MRONJ among denosumab-treated cancer patients is similar to zoledronate users [8].

Based on the literature review, even if the patients treated with oral or intravenous BPs or denosumab for osteoporosis present a real risk of ONJ, this probability remains very low [27–31].

Regardless the therapeutic indication, the duration of BPs therapy is a risk factor for developing ONJ. Studies showed that a longer BPs therapy increases the incidence of developing ONJ [8].

Among local factors, dentoalveolar surgery is considered a major risk factor for ONJ. Tooth extraction is reported as a contributing factor in 52% to 61% of cases. MRONJ appear more likely in the mandible (73%) than in the maxilla (22.5%), but also can affect both jaws. Periodontal disease and/or periapical pathology are also risk factors [8].

Regarding the demographic factors, a variable higher prevalence of ONJ in the female population is reported. This can likely be a reflection of the therapeutic indication (breast cancer, osteoporosis) [8].

Other drugs used as corticosteroids or different medical conditions, such as diabetes mellitus or anemia, are associated with a high possibility to develop MRONJ [32, 33].

To diagnose ONJ, very important elements are the history of the disease and clinical appearance. Even so, before the osteonecrosis become clinically evident, the patient could present different symptoms and signs like pain, mucosal congestion, erythema, mucosal ulceration or tooth mobility. In most cases, these complications have been described in dental extraction sites. The necrotic bone can be asymptomatic for long periods, but after a silent developing the patient may accuse pain and jawbone is exposed. In addition, the infections can aggravate the bone exposure.

BRONJ is a relatively new and serious medical condition and the treatment is very challenging for the oral and maxillofacial surgeons.

The majority of opinions found in the literature support teamwork in the treatment of patients who benefit from antiresorptive or antiangiogenic therapy. Before using any antiresorptive therapy, in order to reduce the risk of ONJ, the patient will be screened for dental health, starting with clinical exam of the oral mucosa. When needed, a radiographic exam will be done. Any site of acute or potential infection will be identified and treated, preventing therefore consequent sequelae that could be exacerbated during the first days of the antiresorptive treatment. The patient needs to be informed about the risk of ONJ and the importance of dental preventive measures. The optimizing the dental health is so important that, if is possible, initiation of antiresorptive therapy will be delayed. Any extractions of non-restorable or poor prognosis teeth and any other dentoalveolar surgery should be performed at this moment of the treatment [34–48].

Cessation of antiresorptive or antiangiogenic therapy in individuals who require dental extractions remains an ongoing area of controversy with limited data to support a drug holiday in both osteoporosis and oncology patients [8].

When working with oncological patients that receive i.v. antiresorptive and antiangiogenic therapy, a weighty matter in the treatment of osteonecrosis is to be aware of the importance of continued oncological treatment. The control of pain, the secondary infection prevention of necrotic bone and the limiting of the extension of bone loss area by raising the individual health education assure a good quality of life for these patients [8].

A clinical staging of the disease was developed in order to categorize BRONJ patients and to offer treatment guidelines. For patients that have received oral or i.v. BP and present a risk to develop ONJ, but there were no clinically or radiological necrotic bone detection, there is no indication for any treatment, except raising the patient health education. For the patients diagnosed in stage 0 disease, that present non-specific signs on clinical exam of oral cavity or on radiographic exam, but without clinical evidence of necrotic bone, pain medication and antibiotics are indicated. For stage 1 asymptomatic patients with no sign of infection, to whom on clinical inspection of oral cavity could be noted exposed areas of necrotic bone or even fistulae, the discontinuation of BP therapy should be considered. If the necessity of the BP therapy is undeniable, clinical follow-up and raising patient health education are the main objectives of maxillofacial clinicians. In addition, the local infections will be prevented using antibacterial mouth washings. Stage 2 patients present exposed and necrotic bone, or fistulae that probes to bone, associated with infection with or without purulent discharge. In these cases, the control of local infection and limitation of tissues inflammation by surgical debridement are the main goals of the treatment. Antibiotics and painkillers are the big helpers, in addition to oral antibacterial washing solutions use. To classify a patient in stage 3 diseases, at least one of the following should be met: (*1*) The pathological jaw fracture should appear on a wider osteonecrosis area that extends beyond the edges of alveolar bone; (*2*) The fistula should communicate extraoral or a communication between oral cavity and antral or nasal area should appear; (*3*) The osteonecrosis should affect the inferior border of the mandible or sinus floor. Besides the treatment options of stage 2 diseases, the resection of affected jaw area should be considered if necessary [8].

In any stage of the disease, all the mobile osseous segments of bony sequestrum should be surgically

removed. In addition, the symptomatic teeth noted within osteonecrosis area should be extracted, since the majority of published papers showed there is no exacerbation of necrotic process after teeth extraction [8].

Conclusions

ONJ is an important complication of BP-treated patients, after minimal dentoalveolar surgical interventions as teeth extractions or, in rare cases, spontaneously. Therefore, optimizing dental health is the main directive in managing patients who will receive BP therapy. The patients receiving intravenous BP have a greater risk to develop ONJ than those treated with oral BP. Moreover, the ONJ appears in a shorter time in patients treated with intravenous BP than those with oral medication. Treatment of BRONJ is directed by the symptoms. Asymptomatic patients require no interventions other the antibacterial mouth rinse and clinical follow-up. Patients with symptomatic disease will require pain medication, antibiotics and surgical debridement or resection. All patients who benefit from antiresorptive or antiangiogenic therapy will most likely develop ONJ in case that future dentoalveolar surgery is needed. That is why raising the dental health education of the potential future BP-treated patients who could realize the great contribution of the prophylactic dental care is essential for them.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Horaţiu Cristian Mânea, Horaţiu Constantin Urechescu and Nicolae Constantin Balica equally contributed to the manuscript.

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