Bisphosphonate-Related Osteonecrosis of the Jaws and Its Array of Manifestations

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Abstract

Purpose Bisphosphonate (BP) therapy in the treatment of bone diseases and malignancy may induce a major side effect known as bisphosphonate-related osteonecrosis of the jaws (BRONJ). A particular view of this condition is reported in this case series investigating eight patients. The aim of the study was to evaluate the BRONJ lesions concerning their aspects and progression. Also, identify if it is possible to predict the degree of severity in these cases.

Methods Patients were evaluated by their condition and systemic health. The lesions were evaluated in clinical and radiographic aspects. The patients were followed-up for 2 years.

Results The patients presented with specific peculiarities, and the BRONJ lesions varied in several characteristics. The BRONJ lesions ranged from simple to severe conditions, and the complicated cases presented with major pain,

swelling, secondary infection and an extensive necrotic area, classified with high grade of severity.

Conclusions The patients presented here confirm the existence of a relation between multiple features and BRONJ and to understand the whole process of aggravation, all systemic and local information have to be taken into account, together with all data related to the BP utilized. Regardless of the low incidence of this side effect in relation to osteoporosis treatment, in some cases, the BRONJ may become a severe condition and compromise the patient's quality of life.

Keywords Bisphosphonate · Cancer · Jaws · Osteonecrosis · Osteoporosis

Introduction

Bisphosphonates (BPs) have become the treatment of choice for various bone diseases in which the osteoclast activity is an important pathological feature, including the two most known indications: osteoporosis and metastatic/osteolytic bone diseases [1]. In the osteoporosis treatment, it is already known that the therapies inhibiting resorption improve bone strength [2] and reduce fracture risk [3]. The BP efficacy in reducing fracture risk, with a favorable safety profile, is well established; however, their long-term use has been associated with reports of undesirable events in some cases [4].

As other medicaments, BP can cause side effects; one of the most important is bisphosphonate-related osteonecrosis of the jaws (BRONJ). BRONJ is defined as the presence of necrotic bone in the oral cavity (sometimes covered by an erythematous mucosa) for more than 6 weeks in patients currently on or who were on BP

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treatment, with no history of radiation therapy in the head and neck region [5]. Recent evidence suggests considering the time of the persistence of the necrotic area for more than 8 weeks, as that is usually the same time for tissue healing in cases of trauma, extractions, and oral surgical procedures [6]. Classified as a serious side effect, with great influence in the patient's quality of life, the etiology and related risk factors of the BRONJ are still partially undefined.

Several features affect the risk and the development process of BRONJ. The most studied factors are: the way of administration of the drug (with the highest risk associated with the intravenous administration), the total time of the treatment, the potency of the BP, the type of treatment, the presence of comorbidities and some local factors, such as oral condition and dental manipulation. Other associated BP properties, like antiangiogenic and immunomodulatory effects, have been also considered in the etiology of BRONJ [7, 8].

The patient's disease and systemic conditions are correlated with the risk of BRONJ. Features like aging, poor oral hygiene, and dental manipulation were correlated with an increase in the risk of osteonecrosis [5, 9]. Furthermore, important microscopic changes in bone, like changes in remodeling and decrease in vascularity, may also increase the risk of BRONJ [7, 9]. In osteoporosis patients, the BRONJ incidence is considered less when compared to cancer patients. Wong et al. [6] reported that the incidence of this side effect related to treatment of osteoporosis can vary, with studies reporting no case of BRONJ until others reported between 2 and 8 %, and mostly of them presented a mean duration of oral BP therapy in around 50 months. For patients in cancer treatment, the incidence was around 3–18 %, among patients who were treated with an intravenous BP [5].

These observations suggested that BRONJ mainly occurred with high doses of BP used in the treatment of bone metastasis but was less, or very rarely induced, by therapeutic doses used in osteoporosis treatment.

Clinical symptoms of BRONJ are mainly pain, swelling, paresthesia, suppuration, soft-tissue ulceration, intra- and/or extra-oral fistula, and loosening of the teeth [9, 10]. Interestingly, although BRONJ can result in clinically important problems for some patients, others only experience intermittent, minimal symptoms [5]. These variations in the clinical findings and symptoms are related to the severity of the cases, impossible to predict in the majority of the cases.

Bisphosphonate-related osteonecrosis of the jaws imposes difficulties concerning diagnosis, staging and treatment. Therefore, the aim of this study was to describe a series of cases with different features in diagnosed

patients with BPs osteonecrosis of the jaws and discuss the features in relation to the severity of the condition, leading to a better understanding of this pathology and the nature of the pathology treated by BP.

Patients and Methods

This study analyzed clinical, radiographic, and demographic data of 8 patients suffering from BRONJ at two Institutions in Brazil between 2008 and 2011. In this period, thirteen cases of BRONJ were attended, but five cases were not included in our series because of the lack of information and follow-up. In all patients, the diagnosis of BRONJ was based on the presence for more than 8 weeks of a necrotic bone area in the oral cavity (not visible in some cases due to the presence of an erythematous mucosa). These patients were currently or had been previously exposed to BP and had no history of radiotherapy on the head and neck. The diagnosis of osteonecrosis was initially made by different dentists, and then the diagnosis of BRONJ was made by two different stomatologists in one of the two institutions.

The study reviewed the medical histories, including comorbid factors; past and current medications; nature and doses of BP; and other variables such as age, gender, smoking, alcohol use, oral condition, and dental history—including use of dental prostheses. We analyzed the BRONJ lesions by location, presence of bony sequestra, symptomatology, soft-tissue infection and image findings (panoramic and standard radiographies and computed tomography in some cases), together with the clinical aspects. The stage of the BRONJ was determined according to criteria established by the American Association of Oral and Maxillofacial Surgeons. The severity of the cases was stipulated by the staging of the disease together with symptoms and other patient complaints, and was considered ranging from the simplest and uncomplicated cases (+ and ++) to the worst and complicated cases (+++ and ++++).

Results

The clinical profile of the patients, including epidemiological data, the oral condition and radiographic findings, BRONJ features, and treatment modalities are shown in Table 1. The patients' ages ranged from 53 to 76 years (mean age 66.7 ± 7.4 years) and included 2 men and 6 women. Four patients were using oral alendronate for osteoporosis treatment (patients 1–4) and four patients were using intravenous zoledronic acid (ZA), none for osteoporosis treatment (patients 5–8). Three of them were

Table 1 Cases of BRONJ

N	Age	G	Medical history	Other medications ^a	Radiographic findings	Stage ^b and severity	Treatment	Follow-up	Type and duration of the BP therapy	Time of complain
1	73	F	Osteoporosis, HBP, osteoarthritis, labyrinthitis, gastritis	Meloxicam, pantoprazole, paracetamol					Oral alendronate for 6 years	1 year
2	65	F	Osteoporosis, HBP, anemia, rheumatoid arthritis, anxiety disorder	Atenolol, amlodipine, erythropoietin, prednisone, simvastatin, bromazepam					Oral alendronate for 4 years	1 year
3	70	F	Osteoporosis, osteoarthritis	Methotrexate, prednisone, calcium, paracetamol					Oral alendronate for 4 years	1 year
4	53	F	Osteoporosis, rheumatoid arthritis	Methotrexate, folic acid, ranitidine omeprazole					Oral alendronate for 4 years	5 months
5	76	M	Prostate cancer	None					IV zoledronic acid for 1 year	4 months
6	62	F	Breast cancer, diabetes	Metformin, thyroxine					IV zoledronic acid for 4 months	2 years
7	72	M	Paget disease, coronary disease, HBP	ASA, atenolol, hydrochlorothiazide, simvastatin					IV zoledronic acid for 1 year	1 year
8	63	F	Breast cancer, metastasis after 12 years of the initial treatment	Fulvestrant, pain killers					IV zoledronic acid for 5 years	5 months
N	Oral condition	Dental manipulation	BRONJ bone site	Signs and symptoms	Radiographic findings	Stage ^b and severity	Treatment	Follow-up		
1	Edentulous, using TRP, good oral health	Tooth extraction 1 year ago	Anterior mandible	Pain, infection, swelling, intra and extra oral fistula	Radiolucent lesion with irregular borders and bony sequestra	3 ++++	Antibiotics and surgical debridement, osteotomy	Pathologic fracture after 2 years		
2	Partially dentate, poor oral health	None	Posterior mandible	Pain, swelling, infection, intra oral fistula, exposed necrotic area	Radiolucent lesion with radiopaque areas and bony sequestra	2 +++	Antibiotics and surgical debridement, osteotomy	2 years without recurrence		
3	Partially dentate, poor oral health	Tooth extraction	Posterior mandible	Pain, infection, halitosis, huge exposed necrotic area, pathologic fracture	Poorly delimited radiolucent area with bone fracture	3 ++++	Antibiotics and surgery	–		
4	Partially dentate, using RDP, good oral health	Tooth extraction 7 months ago	Posterior mandible	Erythematous swelling area with pus discharging, no bone exposed	Poorly defined radiolucent area	0 +	Antibiotics, use of antibacterial rinse	2 years without recurrence		
5	Partially dentate, poor oral health	Tooth extraction 4 months ago	Posterior maxilla	Slight discomfort, opened tooth socket	None	1 +	Antibiotics and surgical debridement, use of antibacterial rinse	2 years without recurrence		
6	Partially dentate, poor oral health	Tooth extraction	Anterior and posterior maxilla	Pain, infection, halitosis, huge exposed necrotic area	Radiolucent lesion with radiopaque areas and bony sequestra	3 ++++	Antibiotics and surgical debridement, osteotomy, confection of prosthesis for the oral nasal communication	2 years without recurrence		
7	Partially dentate, using RDP, poor oral health	None	Posterior mandible	Pain, exposed necrotic area	Radiolucent area	1 +	Antibiotics and surgical debridement	1 year without recurrence		
8	Partially dentate, using RDP, Poor oral health	Tooth extraction 6 months ago	Anterior maxilla	Exposed necrotic area	Radiolucent lesion with radiopaque areas	1 +	Antibiotics and surgical debridement	6 months without recurrence		

M male; F female; G gender; HBP high blood pressure, IV intravenous; RDP removable dental prostheses; TRP total removable prostheses, ASA acetyl salicylic acid

^a Using or used recently^b Stage of BRONJ according to the American Association of Oral and Maxillofacial Surgeons

smokers, and six presented with poor oral health including the presence of dental plaque and calculus.

At the time of the BRONJ diagnosis, all the patients using oral alendronate were in a scheme of 70 mg per week, ranging from 4 to 6 years. All the patients using ZA were in a scheme of one intravenous administration per month for bone metastasis, ranging from 4 months to 5 years, except patient 7, who received only one administration of ZA for Paget disease for 1 year. Also, all patients were using other medicaments for other comorbidities, except for patient 5, who had been on chemotherapy for cancer treatment, but at the time of the examination in our service was without any use of medicaments.

The BRONJ lesions highly varied. Patient 1 presented with an intra- (Fig. 1A) and extra-oral fistula (Fig. 1B) without a visible necrotic bone area in the oral cavity. A

tomography scan (Fig. 1C) allowed us to identify an extensive necrotic area in the mandible. Patient 2 (Fig. 1D), presented with several risk factors such as corticosteroid use, smoking and poor oral health, and revealed an extensive necrotic area, with major pain; but, presented a great recovery 2 years after the treatment without recurrence and with no complaints (Fig. 1E). Patient 3 (Fig. 1F) developed the worst case of BRONJ in this series, with a pathologic fracture (CT tridimensional reconstruction—Fig. 1G) and a difficult management. She received oral BP during 4 years, and also presented an important comorbid disease and took immunosuppressive drugs. Patient 4 developed BRONJ without an exposed necrotic area (Fig. 1H), presenting a swelling covered by an erythematous mucosa; despite the use of BP for 4 years and the association with rheumatoid arthritis, the case was simple

Fig. 1 Patients in oral alendronate treatment. Patient 1—**A** Intraoral fistula in mandible. **B** Extraoral fistula beneath the chin. **C** Computed Tomography scan revealing a hypodense lesion in mandible. Patient 2—**D** Intraoral exposed necrotic area in mandible. **E** 2 years follow-up. Patient 3—**F** Intraoral exposed necrotic area in mandible.

G Tridimensional reconstruction of the Computed Tomography scan revealing a pathologic fracture in mandible. Patient 4—**H** Intraoral nodule covered by an erythematous mucosa in mandible. **I** 2 years follow-up

Fig. 2 Patients in intravenous zoledronate treatment. Patient 5—**A** Intraoral exposed necrotic area adjacent to the tooth extraction socket. Patient 6—**B** Intraoral huge exposed necrotic area in maxilla.

Patient 7—**C** Intraoral exposed necrotic area in mandible. Patient 8—**D** Intraoral exposed necrotic area in maxilla

and resolved well (Fig. 1I). Patient 5 (Fig. 2A) developed a simple case of BRONJ with an excellent recovery. Patient 6 (Fig. 2B) used intravenous ZA, presented several other risk factors and developed an extensive and complicated BRONJ with communication between the oral and nasal cavity. Patient 7 (Fig. 2C), developed a spontaneous BRONJ in the posterior mandible, a region not directly involved in the masticatory function, without contact with the removable dental prosthesis; the patient presented no major symptom and recovered well after treatment. Patient 8 (Fig. 2D), who received ZA for 5 years and had severe comorbidities such as metastasis in the femur and cervical spine, a smoking habit, and deleterious local oral conditions such poor oral health, developed a focal necrosis area without any major symptoms.

About the BRONJ treatment, all patients received antibiotics (Amoxicillin prescribed first in all cases, and association of Ciprofloxacin in two cases) and were followed until the resolution of the lesion.

Discussion

This study reports a case series showing variations between patients who developed BRONJ, focusing on specific characteristics and features found in each case. It appeared that patients who develop this side effect under BP therapy could not be allocated in a generic group. Some features were common between them, but the severity of cases

showed a wide range. In this way, the patient characteristics, as well as the specific properties of the BP, including type, dose, duration, and other related aspects, should be considered together in the diagnosis, staging and treatment of this collateral effect.

In contrast to previous reported observations [9], our case series was characterized by a same proportion of osteoporotic patients as cases of other bone diseases (bone metastasis and Paget disease of bone).

One major interesting point in our study was the great variation among the four patients under oral alendronate (patients 1–4) and among the four patients under ZA (patients 5–8). Despite receiving the same BP by the same way of administration, in both groups the variety in the clinical features and evolution of the cases revealed an inconstancy in the course of the disease. For instance, 3 of the osteoporotic patients taking oral BP developed complicated cases, and, in contrast, 3 patients who had received intravenous BP, except patient 6, developed not severe cases. Patient 6 was characterized by two major risk factors (diabetes and smoking habit), which could favor the occurrence of the BRONJ and aggravate the lesions. In the same way, Watters et al. [10] evaluated 109 patients with BRONJ and described an association between the progression of the disease and diabetes or smoking. Also, Yoneda et al. [9] reported that smoking and alcohol not only increased the incidence but also exacerbated the severity of BRONJ.

Concerning the time of complain, it was very difficult to identify certainly the initiation of the symptoms in some

cases, also, this time varied highly between the patients, complicating the establishment of a correlation of the duration of the symptoms with the duration of the BP treatment. In some cases, the osteonecrosis occurred with a short period of BP therapy, as in patients 5 and 8 under intravenous treatment.

Several series of BRONJ have been reported in the literature and the association of risk factors or other variables analyzed with the development and the progress of the oral lesions, as type of the BP, diabetes, smoking, teeth extraction and others [10–12]. Nevertheless, a possible correlation between the severity of the cases with the patient's condition and the specific properties of the BP remains poorly understood. Therefore, the question is whether the nature, the way of administration of the BP and the duration of the therapy may aggravate BRONJ by itself.

It was already reported that low-dose BP therapy given to osteoporotic patients will result in moderate lesions which may resolve [4], in contrast to patients receiving high doses of IV BPs that could develop the worst cases [13]. However, our case series did not reveal this tendency in all cases analyzed. Among the 4 osteoporotic patients, 3 developed severe BRONJ.

Another point which must be taken into account is the total dose of BP administered. The cumulative dose depends on both the dose and the duration of the treatment. In our patients, the worst case evolution among the users of oral BP received the highest cumulative dose. Patient 1 took alendronate for 6 years and continued the alendronate treatment after the occurrence of BRONJ, even with an important complication, as a pathologic fracture, 2 years after the first manifestation. It was noted that all severe cases in osteoporotic patients have taken BP for a long time, more than 4 years (patients 1, 2 and 3).

Regarding the potency of BPs, it is known that ZA is one of the most potent BP in clinical use [14]. Interestingly, in our study three patients receiving this drug developed uncomplicated BRONJ. Although, it is important to emphasize that patient 7 who received only one injection for 1 year, for the treatment of Paget disease, and the one who developed the most complicated case (patient 6), also presented multiple risk factors condition. In addition, patient 6 was very confused about her health condition, and did not provide information about a possible previous use of other BP and when symptoms exactly started. From these observations, it seems that the duration of treatment and consequently the cumulative dose influenced the severity degree rather than the nature or the way of administration.

About others risk factors, it was also observed that patients who developed BRONJ, and also had the highly severe cases, had other risk factors such as diabetes or smoking. Moreover, the use of steroid/immunosuppressive drugs seemed to favor secondary infection. In a review,

Yoneda et al. [9] reported a double risk in cases of diabetes, obesity, smoking, anticancer therapy, steroid therapy, or poor oral health.

Considering dental manipulation, Mozzatti et al. [15] reported no case of BRONJ in 700 patients in oral BP treatment, however, they proceeded with a delicate surgery extraction or nontraumatic avulsion of the teeth. Yet, Kato et al. [11] reported 4 sites of BRONJ after 65 teeth extractions in 20 patients, but they related the worst healing process to previous periodontal disease. In our series, 6 patients had a tooth extraction but the technic used was unknown, also, an interesting fact was that two patients did not report any dental procedures in the BRONJ area. Anyway, it is important to emphasize that BRONJ patients always must be analyzed considering all the signs, symptoms and features mentioned above; one factor alone, i.e. the tooth removal, cannot always predict the severity of BRONJ.

Regarding treatment, all of our patients demonstrated satisfactory recovery with an improvement in life quality, and pain relieved in all cases. Even with patient 1, who developed a pathologic fracture after the first BRONJ treatment, the therapeutic approach was considered good in the beginning, and as discussed, the recidive could be associated with continue BP treatment for more than 2 years.

In conclusion, the mechanism of the BRONJ development remains unknown, but from our observations, this probably results from the association of several factors. The wide variability in the cases reported shows that this side effect presents various degrees of severity, and, to understand the whole process of aggravation, it has to be taken into account all systemic and local information, together with all data related to the BP utilized. Whereas the risk of BRONJ in osteoporotic patients receiving oral BP is low, it seems that it depends on the duration of the treatment, the association with other risk factors such as diabetes, smoking habit and poor oral condition, and also, could determine the degree of severity, with some cases becoming a severe condition. All these factors must be evaluated before the initiation of BP treatment.

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Conflict of interest None.

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