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Role of Dental Surgery in the Pathogenesis of BRNOJ: An Observational Report of 24 Cases

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Abstract

Background: Most of the patients affected by BRONJ are oncologic patients that frequently assume high doses of bisphosphonate (incidence 1% to 15%), while the incidence in ostenecrosis patients is estimated at 0.001% to 0.01%, due to the lower dose of these drugs. Among the risk factors for BRONJ development, oral surgery procedures seem to play an important role, so that the prevention strategies include elimination or stabilization of oral disease prior to undertaking a protocol of antiresorptive therapy with BPs.

Materials and Methods: Clinical and radiological evaluation of 24 patients with BRONJ was performed in the period between 2011 and 2014. Data about age, sex, systemic pathology and modality of the pharmacological therapy with BPs were collected. The medical history and occurrence of oral surgery procedures were annotated. A protocol of tertiary prevention consisting of antibiotic therapy or/and surgical treatment was also undertaken.

Results: The observed group was composed of 13 males and 11 females with an average age of 73,1 years old. A history of oral BPs administration emerged in 6 (25%) patients; one case (4%) was treated with intramuscular injections, while the other 17 (71%) patients reported intravenous treatment. The mean duration of treatment with oral BPs was 44.8 months, whereas the intravenous treatments lasted 29.8 months in average. The most used molecule was zoledronic acid. Only 8 (33.3%) patients had undergone a previous oral procedure. In 22 cases a medical treatment was chosen with appropriate antibiotic therapy.

Conclusion: The present study showed that dental surgery actually has a marginal role in the pathogenesis of BRNOJ, because minimally traumatic extraction technique, removal of bone edges and mucosal wound closure probably reduce the incidence of BRNOJ after tooth extraction.

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Introduction

The definition of Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ) was formulated for the first time in 2007 by the American Association for Oral & Maxillofacial Surgery as "the presence of an area of exposed necrotic bone in the oral cavity that does not heal within 8 weeks in a patient who was receiving or had been exposed to a Bisphosphonates (BP) and who has not received radiation therapy to the craniofacial region" [1].

The categories subjected to the risk of developing BRONJ are:

Cancer patients treated mostly with intravenous BP for treatment or prevention of bone lesions and represents the group that includes the majority of BRONJ cases [2]; not cancer patients (predominantly with osteoporosis or osteopenia): the number of patients that develop osteonecrosis is significantly lower than in the first category [3].

The frequency of BRONJ among cancer patients is estimated to range from less than 1% to 12% of patients, with higher percentages in those that reported a history of a dental surgical procedure, while in patients who take bisphosphonates for their treatment of osteoporosis the frequency is estimated to be between 0.01% and 0.04%, increasing to 0.34% in patients that underwent tooth extractions [3,4]. However, the incidence data based on larger sample sizes are lacking. According to the scientific literature data, the average risk of BRONJ after a long treatment with intravenous BP in cancer patients seems to vary between 1% and 10% after 2 years of treatment [5,6]. In particular,

Table 1: BRONJ manifested in the upper maxilla.

NO	sex	Age	BRONJ onset	BP	Mode of administration	Start of the treatment with BPs	End of the treatment with BPs	Systemic pathology	Oral surgery intervation	Site of BRONJ	BRONJ treatment	Outcome	Date follow-up examination
1	M	85	November-12	BONIVA®	oral	Dec-07	Apr-12	osteoporosis and vertebral collapse	Extraction	Mandible	Antibiotic therapy	Healing	18/02/2013
				Vantavo®	oral	Apr-12	Nov-12						
2	F	83	November -12	AREDIA ®	oral	Feb-05	Nov-12	osteoporosis	Extraction		Antibiotic therapy	unknown	
3	M	75	September-12	AREDIA ®	ev	Jenuary 12	Oct-12	multiple myeloma	Extraction	Mandible	Antibiotic therapy	unchanged	8/4/2013
4	M	72	February-12	Zometa®	ev	Jenuary 2010	Jun-11	multiple myeloma		mandible	Antibiotic therapy	Improved	9/5/2012
5	M	80	February-12	Zometa®	ev	Jul-10	Feb-12	multiple myeloma		mandible	Antibiotic therapy	Unchanged or worse	4/6/2012
6	M	65	January 2013	Enantone®	ev	Mar-10		Proste cancer with bone metastasis		mandible	Antibiotic therapy	Unchanged	17/06/2013
				Zometa®	ev	Apr-12	Oct-12	osteoporosis					
7	F	72	Febquray-14	Fosavance®	os	Apr-05	Apr-10	osteoporosis		mandible	Antibiotic therapy	A new sequestration	27/7/2014
8	F	62	January 2013	Zometa®	ev	Sep-11	Jenuary 2013	multiple myeloma		Mandible	maxillofacial surgery	Healing	1/6/2014
9	M	69	Febuavary-13	Zometa®	ev	Jul-05	Sep-12	multiple myeloma		Mandible	Antibiotic therapy	Improved	9/5/2013
10	M	67	March-13	Zometa®	Ev	Sep-12	Mar-13	Prostate cancer with bone metastasis		mandible	Antibiotic therapy	Healing	20/02/2014
11	F	80	September-13	CLODY ®	Im	September 20120	Sep-13	Osteoporosis	Extraction	Mandible	Antibiotic therapy	Death	Dec-13
12	F	81	May-13	zometa®	ev	Oct-12	May-13	Metastatic breast cancer	Extraction	Mandible	Antibiotic therapy	Healing	Jul-13
		82	March-14	zometa®	ev	Jul-13	Mar-14		Extraction	Maxilla	Antibiotic therapy	Unchanged	Jul-14
13	f	69	June-13	Fosavance®	os	Feb-12	Jun-13	osteoporosis		Maxilla	Antibiotic therapy	Improved	10/11/2013
14	F	75	September-13	Fosavance®	os	Sep-11	Sep-13	osteoporosis		Mandible	Antibiotic therapy	Unchanged	10/12/2013
15	F	61	3/10/2013	Boniva®	os	Settembre 2011	Settembre 2013	osteoporosis		mandible	Antibiotic therapy	Unchanged or worse	3/4/2014
16	M	80	March-13	zometa®	ev	Feb-08	Feb-13	Prostate cancer with bone metastasis		mandible	Antibiotic therapy	Unchanged or worse	24-3-2014
17	F	53	November-11	Zometa®	Ev	Apr-10	Dec-11	Metastatic breast cancer		Mandible	Antibiotic therapy	unknown	missed appointment
18	M	86	October-13	Zometa®	ev	Dec-10	Oct-13	multiple myeloma	Extraction	Maxilla	Antibiotic therapy	unchanged	20/02/2014
19	M	64	September-13	Zometa®	ev	Feb-10	Feb-11	Metastatic kidney cancer	Extraction	maxilla	Antibiotic therapy	Improved	4/11/2013
20	M	64	December-13	Zometa®	ev	Jenuary 2006	Jul-06	multiple myeloma		Mandible	Antibiotic therapy	Unknown	
21	M	86	Febauary-14	Zometa®	ev	Feb-12	Feb-14	Prostate cancer		mandible	Antibiotic therapy	Unchanged or worse	18/05/2014
22	F	79	March-14	Zometa®	ev	Apr-05	Apr-06	Metastatic breast cancer		maxilla	Antibiotic therapy + surgical curettage	Unchanged	4/8/2014
				Bondronat®		Jenuary 2007	Apr-08						
				Zometa®		Apr-09	Sep-13						
23	F	67	January 2014	Zometa®	ev	Jenuary 2010	Jenuary 2014	Metastatic lung carcinoma		mandible	Antibiotic therapy	Unchanged Death in july	31-3-2014
24	M	80	June-14	Zometa®	ev	Jun-08	Mar-09	Prostate cancer with bone metastasis	Extraction	Mandible	Antibiotic therapy	Unknown	
				Zometa®	Ev	Nov-09	May-13						

the risk seems to be directly proportional to the cumulative dose of the administrated drug [7]. The BPs for the treatment of cancerous lesions to the bone may be distinguished in three generations. The first generation includes the non-nitrogen containing clodronate, the second generation includes the nitrogen containing group such as pamidronate and ibandronate and the third generation that consists of molecules containing a nitrogen ring structures, such as zolendronate [5]. The risk of BRONJ seems to be higher for zoledronic acid, when compared to pamidronate, while no definitive data are available for intravenous ibandronate [8]. Regarding patient-related risk-factors that predispose to the development of ONJ some local and systemic factors have been discussed. Among these, dento-alveolar surgery, a poor dental status, the age, gender and ethnicity seem to play a significative role [9]. Several studies have shown the correlation of the different types of cancer and the risk of BRONJ [9]. Nevertheless, no conclusive result has been provided yet [5]. One of the peculiarities of BRONJ is the prevalent localization to the maxillary bones. This could be due to a higher jaw turnover compared to the remaining skeleton [10], a terminal vascularization of the jaw, peculiar microflora/biofilm of the oral cavity or the characteristic dento-alveolar interface that may predispose to bone exposure, mainly due to the oral procedures [11]. Regarding the BRONJ therapy, there are several protocols that consist either in a conservative medical treatment or in a surgical treatment associated with the medical one and the choice is usually made according to the BRONJ stage [12-14]. The aim of the present paper is to report the marginal role of oral surgery in the pathogenesis of the BRONJ.

Materials and Methods

The cases reported in this study consist of patients with BRONJ visited between November 2011 and October 2014 at Stomatology ambulatory of the Scientific Institute of Hospitalization and Care "Casa Sollievo dalla Sofferenza" of San Giovanni Rotondo, Italy (Figure 1A-D). The study was conducted in accordance with the Helsinki Declaration and the guidelines of good clinical practice and was approved by local Ethics Committee (session of 8-7-2010, protocol N° 8547/08 of 6-8-2010). Informed consent was regularly acquired from patients prior to participation in the study. Patients with lesions compatible with the diagnosis of osteonecrosis of the maxillary bones, defined according to the currently accepted criteria were considered for the inclusion in the present study [15]. In particular, the presence of symptoms and signs, such as pain, and soft-tissue swelling with a history of BPs suggested a suspected BRONJ diagnosis.

The inclusion criteria were:

- patients with an age above or equal to 18 years old;
- patients affected by an oncological pathology who are in treatment with BPs or have been treated with BPs in past;
- Patients who are or have been treated with BPs for not cancer pathologies.
- The exclusion criteria were:
- patients who received radiotherapy (previous or in progress) of head and neck region;
- patients with concomitant neoplasm of the maxillary bones;
- patients who received supplementation of calcium and vitamin D at the time of enrollment and during therapy with BP;
- HIV+ subjects;
- HCV+ subjects.

All types of BPs and every mode of administration were considered.

Every patient was introduced in a protocol including an initial clinical examination, associated with radiographic examinations, among which were Ortho Pantomography (OPT), Computerized Tomography (CT) of the facial bones and CT Dental scan. General data about the age, gender and the systemic diseases were collected. Anamnestic data regarding the assumption of BPs (the start of the treatment, pharmaceutical molecule, mode, duration and, eventually, suspension of administration) and data about occurrence and localization of osteonecrosis were annotated. An eventual history of previous stomatologic interventions was also considered. All the patients with acclaimed diagnosis of BRONJ were subjected to a treatment protocol consisting of medical or surgical intervention. A follow-up management was defined, based on the outcome of the therapy. A descriptive statistical analysis was performed on the collected data.

Results

In the considered period a total of 24 patients, 13(54%) males and 11(46%) females, with BRONJ were detected and treated. The middle age was of 73.1, ranging from 53 to 85 years old at the moment of BRONJ diagnosis. A history of oral BPs administration emerged in 6 (25%) patients; one case (4%) was treated with

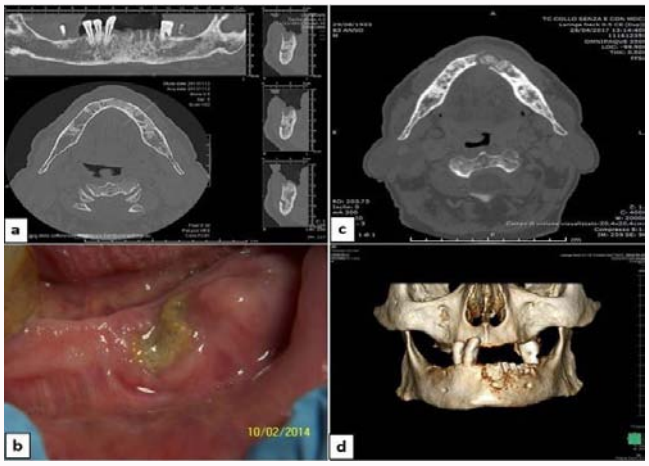

Figure 1: a) The initial computerized tomography (CT) of the facial bones reveals mandibular bone trabeculation broadly and markedly not homogeneous with areas of extensive osteo-rarefaction on both sides. In the median and left paramecia site the edentulous alveolar crest appears not homogeneous, with jagged edges, irregular areas of bone sclerosis, interruption of the cortical profiles and periostal reactive thickening on the vestibular side; b) Clinical appearance of bone exposure in the left paramecia area of the mandible persisted for 3 months of therapy; c) CT of the facial bones without and with contrast medium performed 4 and a half years later reveals marked osteonecrosis alterations of the mandible bone corresponding to the area of missed teeth, with marked morphological and structural change? The necrotic bone affects the dental alveolus that appears no longer in continuity with the rest of the mandible. An edema of the soft tissues is associated; d) Three-dimensional reconstruction of the CT Dentals can of the figure1c.

intramuscular injections, while the other 17(71%) patients reported intravenous treatment. Oral treatments were performed in patients with osteoporosis, while intravenous treatments were prescribed in cancer patients and in particular: in 7 cases for multiple myeloma, in 5 cases for prostate cancer with bone metastases, in 3 patients for the treatment of metastatic breast cancer, in 1 case for lung carcinoma and one for kidney carcinoma. The mean duration of treatment with oral BPs was 44.8 months, whereas the intravenous treatments lasted 29.8 months on average and in all cases the suspension of the treatment was carried out at the time of the BRONJ occurrence. As regards the pharmaceutical preparation, the most used molecules were: zoledronic acid (ZOMETA®) reported in 17 patients, Alendronic acid and Cholecalciferol (Fosavance®) in three cases and Ibandronate sodium (BONIVA®) in two patients. Only 8 (33.3%) patients had received a previous tooth extraction or surgical procedure, and in these cases, the BRONJ manifested on average after 6 months (with a minimum of 1 and a maximum of 12 months) from the oral procedure. Regarding the site of the necrosis, in 19 cases the mandibular bone was involved, while in the other 5 patients the BRONJ manifested in the upper maxilla (Table 1). In 22 cases a medical treatment was chosen with appropriate antibiotic therapy, in one case maxillofacial surgery was performed and in another case a surgical curettage was associated with the antibiotic administration. At the follow up examination that was carried out on average after 5 months from the start of the osteonecrosis treatment, only 4(16,6%) cases manifested a complete remission of the lesion, 4(16,6%) patients manifested an improvement, while in 11(45,8%) cases the bone lesions seemed to be unchanged or worsened in comparison with the initial appearance. In 5(20,8%) patients it was not possible to observe the evolution of the lesion due to the missed follow-up visit or death (in one case).

Discussion

Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ) is a drug-related adverse condition that may negatively influence the life quality of the affected patients [16]. BPs are a drug group employed in treatment of skeletal pathologies, in particular they have been demonstrated to reduce bone events in patients affected by oncologic and haematological diseases [17]. BPs are nowadays used also in the treatment of benign osteometabolic diseases, as well as for osteoporosis prevention [18]. BRONJ cases have been reported in all categories of patients treated with aminobisphosphonates, trough with different frequencies [19]. No reliable epidemiological data on BRONJ are currently available. The current lack of epidemiological data originates from several factors, including the recent recognition of the disease and a limited reporting of cases to the pharmacovigilance register. An important problem, even today, is a lack of awareness of the management of the disease by many operators (primary care physicians, oncologists, dentists, etc.) [20] and a lack of patient knowledge [21]. Moreover, the identification of patients with BRONJ is also influenced by the diagnosis that, nowadays, is based mainly on the presence of exposed bone in the oral cavity. The need to ascertain the persistence of necrotic bone for at least 8 weeks would also lead to late access to the necessary therapies and considerably limit their potential efficacy. For this reason it should be considered that many patients treated with BPs developing BRONJ show signs and symptoms, at least in the initial phase, different from the bone exposure [22,23]. Therefore, if we consider this finding as indispensable for the suspicion of BRONJ, in many cases we lose the possibility of an early diagnosis, increasing the risk of underestimating the incidence of the disease [24]. These factors should be known above all by private dentists, so that the patients at risk can be identified and treated appropriately. Furthermore, it is necessary to take into account the risk factors that help distinguish high and low risk patients, with consequences both in terms of prevention and early diagnosis. Unfortunately, there are currently no definitive data on risk factors. On the basis of the data present in the literature, we can state that with regard to drug-related and systemic risk factors:

- in cancer patients, zoledronic acid appears to pose a statistically higher risk of BRONJ than other molecules [5,7,8]; among other things, as was also shown by our study, zoledronic acid is also the most widely used molecule, followed by alendronate and ibandronate;

- the intravenous administration, compared to the oral intake, exposes the patient to a greater risk of developing BRONJ, but this is closely linked to their use in cancer patients [2,6]; however, as also emerged from our experience, patients taking oral BPs are not exempt from the risk of BRONJ and this should not be underestimated when making therapeutic and/or preventive considerations.

- the duration of intravenous aminobiphosphonate treatment is directly proportional to the risk of developing BRONJ, as the duration of treatment appears to be comparable with the total dose of drug administered [5]; the average time for the onset of BRONJ in our cases was about 30 months from the start of administration of intravenous BPs and about 45 months for oral BPs. These data are almost identical to those present in the literature [25]. Regarding the underlying disease, most of our cancer patients, who developed BRONJ, were affected by multiple myeloma, followed by those with prostate cancer. However, the literature data are still controversial about whether the risk is related to the underlying disease [5,6]. Oral surgery procedures seem to be those most frequently associated with the development of BRONJ [26] and dental extraction is the most common immediate precipitating BRONJ risk factor [27,28]. Since Marx et al. [29] first reported BRONJ, this condition has been known as a complication in patients receiving tooth extractions during BP therapy. Tooth extraction has been indicated as the main trigger for BRONJ by several authors [29-31]. In 2010 Filleul et al. [31] concluded that tooth extraction was the main trigger factor in 67% of 2400 BRONJ cases. Also a position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS) concurred that tooth extraction was a common predisposing event, with 52% to 61% of patients reporting tooth extraction as the precipitating event [32]. BRONJ after tooth extraction is believed to have an overall incidence rate of 0.09% to 0.34% [3], and a recent estimate of the risk of BRONJ in patients exposed to oral BPs after tooth extraction was 0.5% [33]. Also a recent report indentified five main events that triggered the development of BRONJ: dental extraction (54 sites, 60%), prosthetic trauma (18 sites, 20%), implant treatment (nine sites, 10%), oro-dental infection (two sites, 2%), and periodontal disease (one site, 1%) [34]. Tooth extraction was the event that most negatively influenced BRONJ staging (OR 1.60, 95% CI 1.00–2.81; P=0.05), in comparison to other events such as prosthetic trauma, implant treatment, oro-dental infection, and periodontal disease [34]. However, in our study only 33.3% of patients had received a previous tooth extraction or surgical procedures, and in these cases, the BRONJ became evident about 6 months after. Also other studies reported a limited role of the oral surgery in the pathogenesis of BRNOJ. In the study of Jeong et al. [35] only 11 patients among 320 osteoporotic patients who underwent tooth extraction, reflecting an incidence rate of 3.44%, developed BRNOJ. For what concern the treatment, in our experience in more than 90% of cases a medical treatment was chosen, adopting an antibiotic administration protocol, considering that the infection is a constant in the clinical manifestation of the BRONJ [36]. It should be noted that today there is no real evidence of the effectiveness of the various molecules, so the choice and use of a particular protocol is based above all on clinical experience [37]. After treatment, only about half of the patients experienced improvement or resolution of the osteonecrotic lesion, while the others had no improvement or showed worsening of the initial condition. Based on our experience, together with the scientific results of the literature, we believe that in many cases, even surgical treatment must be associated with antibiotic therapy [7,38].

Conclusion

The present study reports data from 24 patients who developed maxillary osteonecrosis following a period of bisphosphonate intake showing that dental surgery actually has a marginal role in the pathogenesis of BRNOJ, minimally traumatic extraction technique, removal of bone edges and mucosal wound closure probably reduced the incidence of BRNOJ after tooth extraction.

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