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Surgery-triggered and non surgery-triggered Bisphosphonate-related Osteonecrosis of the Jaws (BRONJ): A retrospective analysis of 567 cases in an Italian multicenter study

Paolo Vescovi [a,*], Giuseppina Campisi [b], Vittorio Fusco [c], Giovanni Mergoni [a], Maddalena Manfredi [a], Elisabetta Merigo [a], Luigi Solazzo [d], Mario Gabriele [e], Giovanni M. Gaeta [f], Gianfranco Favia [g], Franco Peluso [h], Giuseppe Colella [i]

[a] Department of Otolaryngological/Dental/Ophthalmological and Cervico-Facial Sciences, University of Parma, Parma, Italy
[b] Sector of Oral Medicine "V. Margiotta", Department of Oral Sciences, University of Palermo, Palermo, Italy
[c] Department of Onco-Hematology, Hospital of Alessandria, Alessandria, Italy
[d] Maxillo-Facial Surgery, ARNAS Ospedale Civico, Palermo, Italy
[e] Department of Surgery, Section of Oral Surgery, University of Pisa, Pisa, Italy
[f] Department of Odontostomatological, Ortodontical and Surgical Disciplines, Second University of Naples, Naples, Italy
[g] Department of Odontostomatology and Surgery, University of Bari, Bari, Italy
[h] Unit of Maxillofacial Surgery and Odontostomatology, San Sebastiano Hospital, Caserta, Italy
[i] Department of Head and Neck Surgery, Second University of Naples, Naples, Italy

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SUMMARY

Invasive local procedures are often reported in clinical history of patients suffering from Bisphosphonates-Related Osteonecrosis of the Jaws (BRONJ) but over 40% of spontaneous forms have been also described in literature.

We compared age, gender, underlying bone disorders, bisphosphonate therapy, clinical features and surgical outcome of 205 cases (36.2%) of BRONJ non surgery-triggered (group 1) with 362 (63.8%) cases of surgery-triggered forms (group 2). Differences between group 1 and 2 were analysed using Mann-Whitney *U* and χ^2 tests. Statistical analysis was performed using STATA 8.

Zoledronate was the most used type of bisphosphonate (63.4% *versus* 69.0%) and the mandible was the most frequently involved site (63.9% *versus* 63.4%) in both groups. BRONJ in group 1 was more frequently multicentric (9.3% *versus* 5%, $p < 0.05$), had a lower clinical stage (45.9% *versus* 13.8% in stage 1, $p < 0.01$) and had a better outcome after surgical therapy (improvement in 74.1% *versus* 58.6%, $p < 0.05$).

The high prevalence of non surgery-triggered forms of BRONJ should be considered by oncologists, haematologists and general physicians who are advised to inform their patients regarding the importance of preventive dental protocols to control the possible causes of osteonecrosis not related to dental invasive procedures.

Introduction

Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ) has been defined as an area of bone exposure in the maxillo-facial region that did not heal within 8 weeks after diagnosis by a health care provider in a patient who was receiving or had been exposed to a bisphosphonate (BP) without history of radiation therapy to the head and neck.[1,2]

Oral intake of BP for the treatment of osteopenia, osteoporosis and Paget's disease has also been found to show a risk of BRONJ development, although lower than that due to intravenous route for multiple myeloma and bone metastases (0.01–0.04% *versus* 0.8–12%, respectively).[2–4] The relative potency and dose of BP play a role in the initiation of BRONJ.[2,5] Bone lesions are sometimes asymptomatic or can be accompanied by fistulas, purulent discharge, pain, alveolar nerve paraesthesia, mobility and loosening of teeth, maxillary sinus involvement and mandibular fracture. Ruggiero et al. proposed a clinical staging system for BRONJ (see Table 1).[6] BRONJ can be localised in the mandible (65%, mainly in the mylohyoid ridge on the lingual surface), in the maxilla (26%, mainly in the palatine torus and in the alveolar ridges) or both (9%).[7]

* Corresponding author. Address: Sezione di Odontostomatologia, Università degli Studi di Parma, Via Gramsci 14, 43100 Parma, Italy. Tel.: +39 0521 292759; fax: +39 0521 292955.
E-mail address: paolo.vescovi@unipr.it (P. Vescovi).

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Table 1
BRONJ clinical staging system according Ruggiero et al.[6]

Stage 1	Exposed bone that is asymptomatic with no evidence of any significant adjacent or regional soft tissue inflammatory swelling or infection
Stage 2	Exposed bone with associated pain, with adjacent or regional soft tissue inflammatory swelling or secondary infection
Stage 3	Exposed bone in patients with pain, infection, and pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border

A clinical variant of BRONJ, whose nature and evolution has not yet been well defined, is the non-exposed type. Clinical features include persistent jaw bone pain, bone enlargement, gingival swelling in absence of significant dental disease and clinical evidence of necrotic bone exposure.[8,9]

The aetiology of BRONJ remains still unknown. The multifactorial pathogenesis is related to many local or general factors including suppression of the bone turnover, inhibition of angiogenesis, soft tissue toxicity, fungal and bacterial infections.[10,11]

In the first case series reported by Marx et al. and Ruggiero et al. more than 70% of BRONJ occurred after tooth extractions or other dento-alveolar surgical procedures (e.g., periodontal surgical treatment, implants).[12–14] In light of this finding several authors and dental associations recommended health care professionals to avoid dental invasive procedures in patients taking BPs.[15,16]

During the bisphosphonate therapy (BPT) a conservative approach is of choice, but in the presence of a dental emergency, invasive surgery cannot be delayed.[17]

When surgical treatment becomes unavoidable, antibiotic prophylaxis with amoxicillin (2 g per day) should be taken.[7,18,19] Positive results with additional preventive procedures such as ozone or low level laser therapy have been reported.[20,21]

In literature over 40% of non surgery-triggered forms of BRONJ – which are not associated with any invasive dental procedure – have been reported. These cases seem connected to dental diseases, local trauma or anatomical abnormalities. However, for some patients it is impossible to identify any possible cause.[22] Bagan et al. reported 9 out of 20 cases of BRONJ without any history of invasive local procedures.[23] Badros et al. reported 22 patients with multiple myeloma affected by BRONJ and 10 of them had not undergone dental extractions in the affected area.[24] Marx et al. reported 50% of "spontaneous forms" of BRONJ associated with oral BPs in patients affected by osteoporosis.[13] Recently, Burr and Allen demonstrated that BPT caused a non-exposed spontaneous bone necrosis in the mandible of a canine model.[25]

Periodic dental follow ups (from 4 months for oncologic to 8 months for non-oncologic patients) are advisable, since BRONJ can develop without any obvious or well known trigger factor.[7] Chronic periodontal pathologies or denture traumatisms may be involved in the development of BRONJ and should be carefully considered in the management of patient in BPT.[7]

Badros et al. reported that in a group of patients affected by multiple myeloma and BRONJ, 53% were not related to invasive dental procedures.[26] These forms had a significantly worse outcome with respect to those related to invasive procedures.

Until now it is not clear whether the two forms of BRONJ have the same clinical course or differ in some features.

This multicenter retrospective 4 year study of 567 BRONJ cases was carried out to (i) investigate differences between the non surgery-triggered *versus* surgery-triggered variants and (ii) increase awareness among oncologists, haematologists and general physicians who are advised to inform and educate their patients about the importance of effective preventive dental protocols.

Patients and methods

Between January 2004 and May 2008, 672 patients with BRONJ referred to the eight participating hospitals (2 in the north, 1 in the centre and 5 in the south of Italy) were considered in the study. Inclusion criteria, according to the BRONJ definition of the American Association of Oral and Maxillofacial Surgeons,[6] were the following:

- patients with exposed bone in the maxillofacial area occurring in the absence of head and neck irradiation and showing no evidence of healing for at least 8 weeks after lesion identification;
- previous or current BPT.

The following data were also recorded:

- gender;
- age;
- underlying bone disorders and co-morbidities (e.g., diabetes and coagulopathy);
- site of the lesions;
- clinical stage (according to Ruggiero staging system,[6] see Table 1);
- type of BP administered;
- time between beginning of BPT and BRONJ development;
- any potential precipitating event (e.g., tooth extraction, implant placement, periodontal surgery);
- outcome after surgical treatment of BRONJ, when performed.

Outcome was evaluated after 6 months from surgical treatment and recorded using Ruggiero 's BRONJ staging system[6] as follows:

- improvement: if the patient showed a lower stage after surgery;
- no modification: if patient showed the same stage before and after surgery;
- worsening: if the patient showed a higher stage after surgery.

Patients were then subdivided into two groups: (group 1) non surgery-triggered BRONJ lesions and (group 2) surgery-triggered BRONJ lesions.

Differences between group 1 and 2 were analysed using Mann-Whitney U test for continuous variables and χ^2 test for categorical variables when indicated. Statistical analysis was performed using STATA 8. $p < 0.05$ was considered significant.

Results

For 105 out of the 672 patients it was not possible to recover any information about precipitating events, therefore these patients were excluded from the study. The age range of the remaining 567 patients with BRONJ (184 men and 383 women) was 28 to 94 years (mean 67.2 ± 10.8 years).

Group 1 (non surgery-triggered forms) consisted of 205 patients (36.2%): 65 men and 140 women. The mean age in group 1 was 67.4 ± 10.5 years. According to their medical records, in 21 cases (10.2%) a prosthetic trauma was present at the site of the lesion and in four cases (2.0%) BRONJ was associated with severe periodontitis. In the remaining 180 cases (87.8%) no precipitating event was recorded.

Group 2 (post-local invasive procedures forms) consisted of 362 patients (63.8%): 117 men and 245 women. The mean age in group 2 was 67.0 ± 11.0 years. BRONJ in group 2 occurred after tooth extraction in 361 cases and after implant placement in one case only.

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Table 2
Underlying bone disorders, co-morbidities and type of bisphosphonate administered.

	Underlying bone disorders				Co-morbidities		Type of bisphosphonate				
	Osteoporosis	Multiple Myeloma	Bone metastasis	Other disorders	Diabetes	Coagulopathy	Pamidronate	Zoledronate	Alendronate	Zoledronate + pamidronate	Other BPs
Group 1	26 (12.7%)	61 (29.8%)	112 (54.6%)	6 (3.0%)	19 (9.3%)	14 (6.8%)	21 (10.0%)	130 (63.4%)	19 (9.3%)	21 (10.0%)	14 (7.3%)
Group 2	52 (14.4%)	142 (39.2%)[a]	155 (42.8%) [a]	13 (3.5%)	27 (7.5%)	29 (8.0%)	17 (4.7%)[a]	250 (69.0%)	32 (8.8%)	27 (7.4%)	36 (10.1%)

[a] $p < 0.05$ *versus* group 1.

Group 2 was characterised by a higher prevalence of patients affected by multiple myeloma and a lower prevalence of patients with bone metastasis with respect to group 1 (Table 2).

In the majority of patients with bone metastasis the native site of the malignancy was the breast (64.3% *versus* 63.9% in group 1 and 2, respectively) and the prostate (22.3% *versus* 20.6% in group 1 and 2, respectively). No significant differences were found in the prevalence of co-morbidities between the two groups of patients (Table 2).

The percentage of patients treated with pamidronate was higher in group 1 in comparison to group 2 (Table 2). Furthermore, in group 1 BRONJ lesions were more frequently located both in the mandible and maxilla when compared to group 2 (Table 3).

The clinical stage of BRONJ lesions is significantly lower in group 1 compared to group 2 (Table 3).

The outcome evaluated after 6 months from the surgical therapy is reported in Table 4. Forty-nine patients of the group 1 had no outcome recorded and 44 patients did not undergo any surgical treatment. Eighty-seven patients of the group 2 had no outcome recorded and 77 patients did not undergo any surgical treatment. In addition, in group 2 there were more patients whose clinical stage of BRONJ remained unchanged in comparison to group 1. Patients in group 1 had a better outcome after surgery compared to patients in group 2.

The surgical outcome for each stage was evaluated in both groups and the results are reported in Table 5. In group 1 there was a trend toward a better outcome with respect to group 2 in the 3 clinical stages, with a significant difference for patients in stage 2.

There were no significant differences between group 1 and 2 with regard to the mean numbers of months of BPT before the development of BRONJ (24.3 ± 18.8 and 25.6 ± 20.3 months, respectively).

Discussion

There is increasing evidence that patients receiving BPT may develop BRONJ following surgical dental procedures but also as a result of periodontal and/or endodontic infections or local trauma. In this multicenter retrospective study, 205 (36.2%) out of 567 patients with diagnosis of BRONJ showed lesions not related to invasive dental procedures.

Group 1 (non surgery-triggered forms) and group 2 (surgery-triggered forms) were similar for gender and age.

Table 4
Surgical outcome.

	Improvement	No modifications	Worsening
Group 1	83 (74.1%)	19 (17.0%)	10 (8.9%)
Group 2	116 (58.6%)[a]	59 (29.8%)[b]	23 (11.6%)

[a] $p < 0.05$ *versus* group 1.
[b] $p < 0.01$ *versus* group 1.

Patients in group 1 were more frequently affected by bone metastasis and less by multiple myeloma compared to group 2. We hypothesised that the better state of health of patients affected by multiple myeloma allows them to receive more dental care (including dental extractions and other invasive procedures such as implants or endodontic–periodontal surgery) compared to the patients affected by bone metastasis. On the other hand, patients with poor health conditions and low life expectancy, such as patients with bone metastasis, often could not receive dental treatments and unresolved infections (endodontic or periodontic) could determine the development of non surgery-triggered forms of BRONJ. A slight but significant difference in the prevalence of pamidronate administration was observed between the two groups. This result is difficult to interpret because, to the best of our knowledge, there is no biological or clinical explanation and further investigations are needed to confirm this finding.

Osteonecrosis in group 1 more frequently involved both the mandible and maxilla than lesions in group 2. This result could be explained by the fact that dentists may be discouraged from performing further surgical procedures in other areas of the jaws after the development of the first appearance of BRONJ.

Non surgery-triggered BRONJ showed a significantly lower clinical stage compared to that caused by invasive procedures. We hypothesised that a bone with impaired metabolism and low potential healing subjected to surgical procedures could be characterised by worse signs and symptoms (and therefore a consequent worsening in the clinical stage). Furthermore, bone necrosis due to BPT could be diagnosed as a complication of tooth extraction and this could postpone a correct diagnosis and, consequently, possible therapy. On the other hand, some dental extractions were performed in the area of underlying osteonecrosis, which could mimic endo-periodontal symptoms.

One limitation of this study is that it has not considered the non-exposed variant of BRONJ.[9] This is due to the fact that when the study was planned (and during the time of data collection from

Table 3
Location of BRONJ lesion and clinical stage.

	Mandible	Maxilla	Mandible + maxilla	Clinical stage			
				Stage 1	Stage 2	Stage 3	ND[c]
Group 1	131 (63.9%)	55 (26.8%)	19 (9.3%)	94 (45.9%)	86 (42.0%)	24 (11.7%)	1 (0.5%)
Group 2	230 (63.6%)	114 (31.5%)	18 (5.0%)[a]	50 (13.8%)[b]	257 (71.0%)[b]	44 (12.2%)	11 (3.0%)[a]

[a] $p < 0.05$ *versus* group 2.
[b] $p < 0.01$ *versus* group 1.
[c] Not determined.

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Table 5
Surgical outcome and clinical stage.

Stage at time of surgery		Improvement	No modification	Worsening
Stage 1	Group 1	40 (72.7%)	11 (20.0%)	4 (7.3%)
	Group 2	17 (63.0%)	8 (29.6%)[a]	2 (7.4%)
Stage 2	Group 1	31 (75.0%)	4 (10.0)	6 (15.0%)
	Group 2	80 (56.7%)[a]	43 (30.5%)[a]	18 (12.8%)
Stage 3	Group 1	12 (75.0%)	4 (25%)	0 (0%)
	Group 2	15 (65.2%)	5 (21.7%)	3 (13.0%)

[a] $p < 0.05$ *versus* group 1.

January 2004 to May 2008) this variant had not yet been introduced into the clinical staging system.[2] Therefore, only BRONJ with exposed bone lesions is considered in this study.

In our study, in contrast to that reported by Badros et al.[26] we found the surgical outcome was more successful for non surgery-triggered forms. One of the possible reasons, according to current literature, is that the surgical outcome of BRONJ lesions diagnosed as low clinical stage is more effective compared to lesions recorded as high clinical stage.[27]

In particular, in group 1 there was a higher prevalence of stage 1 lesions and a lower prevalence of stage 2 lesions compared to group 2. The outcome in the sub-groups of patients within the same stage was also evaluated: spontaneous forms recorded better outcomes suggesting that some possible variables in the group 1 could positively affect the outcome compared to the surgery-triggered forms.

According to other studies, surgical related lesions are more frequent than non surgery-triggered forms.[2] However, the number of the latter forms reported has increased in the last 3 years. The frequency of non surgery-triggered reported forms may today be higher than in the past because BRONJ has sometimes been misdiagnosed and confused with dental disease or even treated with teeth extraction. The result is a non-healing socket then subsequently diagnosed as BRONJ. In some of these cases it is likely that the bone necrosis was already present before tooth extraction. A thorough analysis of dental history could be useful in distinguishing BRONJ correlated to invasive procedures from non surgery-triggered BRONJ treated by dentists as a dental disease.

There is no way to foresee the risk of BRONJ development associated with either leaving or extracting an unsalvageable infected tooth in a patient during BPT. The choice is up to clinicians who need to evaluate the risks and benefits in each individual case.

The high frequency of non surgery-triggered forms of BRONJ is noteworthy and should be considered by oncologists, haematologists and general physicians, who are advised to inform their patients about the importance of an effective preventive dental protocol. Possible causes of BRONJ not related to invasive dental procedures should be eliminated before starting BPT as already recommended for dental extractions or surgical procedures.

Conflict of interest statement

None declared.

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