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Original article

Osteonecrosis of the jaws in patients assuming oral bisphosphonates for osteoporosis: A retrospective multi-hospital-based study of 87 Italian cases ☆

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ABSTRACT

Background: Bisphosphonates (BPs) are currently the chief drugs for the prevention/treatment of osteoporosis; one of their adverse effects is the osteonecrosis of the jaw (BRONJ). The primary endpoints of this multi-center cross-sectional study are: i) an observation of the clinical features of BRONJ in 87 osteoporotic, non-cancer patients; and ii) an evaluation of their demographic variables and comorbidities.
Methods: 87 BRONJ patients in therapy for osteoporosis with BPs from 8 participating clinical Italian centers were consecutively identified and studied. After BRONJ diagnosis and staging, comorbidities and data relating to local and drug-related risk factors for BRONJ were collected.
Results: 77/87 (88.5%) patients in our sample used alendronate as a BP type; the duration of bisphosphonate therapy ranged from 2 to 200 months, and 51.7% of patients were in treatment for ≤38 months (median value). No comorbidities or local risk factors were observed in 17 (19.5%) patients, indicating the absence of cases belonging to BRONJ forms triggered by surgery. BRONJ localization was significantly associated with age: an increased risk of mandible localization ($p = 0.002$; OR = 6.36, 95%CI = [1.89; 21.54]) was observed for those over 72 yrs. At multivariate analysis, the increased risk of BRONJ in the mandible for people over 72 yrs (OR′ = 6.87, 95%CI = [2.13; 2.21]) was confirmed for a BP administration >56 months (OR′ = 4.82, 95%CI = [2.13; 22.21]).
Conclusion: Our study confirms the fundamental necessity of applying protocols of prevention in order to reduce the incidence of BRONJ in osteoporotic, non-cancer patients in the presence of comorbidities and/or local risk factor as well as, less frequently, in their absence.

1. Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is described by Bedogni et al. [6] as an adverse drug reaction consisting of the progressive destruction and death of bone that affects the mandible or maxilla of patients exposed to the treatment with nitrogen-containing bisphosphonates, in the absence of a previous radiation treatment. Clinically, the most frequent sign is bone exposure even if different symptoms and minor signs (i.e. pain, hypoesthesia/paraesthesia, fistula, abscess, swelling, trismus) should raise suspicions of BRONJ. Early diagnosis is still essential for patients and clinicians, given the slight hope of restitutio ad integrum in BRONJ patients.

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BRONJ prevalence in cancer patients (range 3–18%) has been the focus of the majority of papers [3,55] to date, whereas the impact of BRONJ in non-cancer patients, with osteoporosis or Paget disease, who receive lower doses of BPs is less known [34,37]. The estimated prevalence of BRONJ in non-cancer (mainly osteoporotic) patients may range from 0.02% to 11% [22–24,29,33,36,42,44,47,49].

Less uniform is the percentage of BRONJ among non-cancer, osteoporotic patients within whole samples also comprising cancer patients: in a multi-center study, a BRONJ frequency of 7.1% in patients treated with oral BP therapy [41] was reported; a frequency of 8.9% of BRONJ after per os BP administration was observed in two Israeli medical centers; and, of all the BRONJ patients in other case series reported in the literature, the percentage of orally-administered bisphosphonate-induced ONJ ranges from 2.5% to 27.3% [58]. In the absence of reliable statistics indicating the number of patients exposed to BPs, it is still not easy to establish the real risk of developing BRONJ for non-cancer patients, also due to the large number of supposed and still unascertained risk factors. Moreover, some authors indicate a notable under-reporting [25] while affirming that BRONJ is becoming more common [30].

Japanese authors [57] have recently identified a risk of <1% for 4129 patients regarding osteomyelitis of the jaw due to oral BP, underlying that the use of BPs may increase the risk of osteomyelitis more than with other osteoporosis medications. Other authors [12] have recently described a total of 310 patients with BRONJ from oral BP, after a Pub-Med-based search of case series with a minimum number of 10 subjects. Reid and Cornish [42] have reported 261 cases of BRONJ in patients who had received oral BP, the majority of whom were treated by the most widely used amino-BP (NBP), that is, alendronate.

Turning to Italy, Lapi et al. [27] evaluated the association between oral BPs prescribed for the secondary prevention of osteoporotic fractures and the rate of BRONJ, discovering an incidence rate of 36.6 per 100,000 person-year. Vescovi et al. [54] published data from a single-center experience in which 19.9% of cases of BRONJ in non-oncological patients were described. An online report by the Italian Drug Regulatory Agency (AIFA) observed 18% of BRONJ warnings related to the use of BPs for osteoporosis in a period from 2001 to 2009 [50]. Favia et al. [16] analyzed a total of 24 BRONJ cases in patients who underwent bisphosphonate therapy for non-cancer disease over a 4 year period.

In our opinion it is necessary to fill the following gaps in knowledge: 1) the incidence and the prevalence of BRONJ in non-cancer osteoporotic patients taking oral NBP; and 2) the nature and entity of risk factors for BRONJ in osteoporotics. BRONJ is capable of reducing QoL in osteoporotic patients and cancer outlives [38], as can be observed in the later stages as: infected and painful necrotic jaw bone, ulcerated, painful, and swollen oral mucosa, chronic sinus tracts and facial deformity, impaired speech, swallowing, and eating. QoL impairments for late stages of BRONJ are similar to the side effects in cancer treatments.

The primary endpoints of the Italian multi-center, cross-sectional study presented in this paper are: i) an observation of the clinical features of BRONJ in 87 non-cancer osteoporotic patients; and ii) an evaluation of their demographic variables and comorbidities.

2. Methods

2.1. Study design

A cross-sectional study was carried out between January 2004 and December 2007 in eight Italian clinical centers (2 in the north of Italy, 1 in the center and 5 in the south).

2.2. Participants

We consecutively and unselectively included 92 osteoporotic non-cancer patients with the following inclusion criteria:

1) the presence of osteoporosis in therapy with BPs;
2) the presence of BRONJ according to the definition of the AAOMS [46]; and
3) the presence of a non-exposed variant of BRONJ [17]
4) age ≥18 yrs.

The exclusion criteria were:

1) the presence of cancer alone or in concomitance; and
2) a history of radiotherapy to the head and neck region.

2.3. Outcomes

The following data were recorded: gender, age, steroid therapy and comorbidities (e.g., diabetes and coagulopathy), type of BP administered and formulation, site of each lesion, clinical BRONJ stage [46], the duration of bisphosphonate therapy at BRONJ presentation, and any potential precipitating event (e.g. dento-alveolar surgery, periodontal disease). Every patient in the study provided informed consent was methodically examined, and a complete medical history was taken. After clinical examination, all patients underwent radiological examinations of the jaws (panoramic radiograph and CT), focusing particularly on alterations of bone architecture with a loss of medullar bone, trabeculation, or increased bone density [7,45].

2.4. Statistical methods

A statistical analysis was conducted, considering two responses of the study: BRONJ localization (coded as maxilla—reference, mandible, mandible and maxilla) and BRONJ stage coded according to AAOMS-Update 2009. The association with local and systemic variables was tested using the χ^2 test or Fisher's exact test, where appropriate. Crude Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated as association measures. To obtain adjusted ORs with respective 95%CIs, the multinomial logistic regression was applied to BRONJ localization and the ordinal logit model was used to identify the BRONJ stage. If variables were significantly associated with the responses in the univariate analysis, they were included in the multivariate models and the duration of administration was included in both models due to its clinical relevance in the study. The age variable was categorized with respect to the median of the analyzed sample. The duration of bisphosphonate administration was categorized into quartiles, and ≤24 months was chosen as a reference category. Alendronate was chosen as the reference type of administered bisphosphonate. A p value ≤0.05 was chosen for statistical significance and the data were analyzed using STATA MP, v. 11.0.

This multi-center study was approved by the Ethics Committee of every unit or department involved and conducted according to the Declaration of Helsinki.

3. Results

3.1. Participants

Data from 92 cases of BRONJ were collected: all patients were female, ranging in age from 53 to 92 yrs (mean age ± standard deviation 70.7 ± 9.7 yrs; median 72). Of this sample, we excluded five (5.4%) patients from the study due to their off-label use of BP (3 for i.m. zoledronate, 1 for i.v. zoledronate plus i.v. pamidronate, and 1 for i.v. pamidronate) and, after confirmation of eligibility, we included and analyzed 87 patients. Within this latter sample, we included fifteen cases (17.2%) in which BRONJ diagnostic criteria by AAOMS (i.e. bone exposure sign) had not been totally matched and they were at stage "0", since at least one of the characteristics of the non-exposed variant of jaw osteonecrosis was present (i.e. fistula, swelling, jawbone pain, mobile teeth, and mandibular fracture), as defined by Fedele et al. [17].

3.2. Descriptive data

Postmenopausal osteoporosis was the main condition necessitating BP therapy (84/87 patients, 96.5%), followed by corticosteroid-induced osteoporosis (3/87, 3.5%). The variables considered are summarized in Table 1.

3.3. Main results

Forty-two patients (42/87, 48.3%) had various comorbidities (e.g. diabetes mellitus, hypertension, HCV-related liver disease, cardiac diseases); thirty-three (37.9%) of these had concomitant local risk factors (Table 2). In twenty-eight cases (28/87, 32.2%) no comorbidities or co-medication were recognized; for seventeen patients (19.5%) no local risk factors or comorbidities were shown.

Regarding BP type, 77/87 (88.5%) patients used alendronate (a weekly dose of 70 mg orally), 7 (8.1%) patients used clodronate (monthly dose of 600 mg i.m.), 2 (2.3%) patients risedronate (weekly dose of 35 mg orally) and 1 (1.1%) ibandronate (3-monthly dose of 2 mg i.v.). Three patients were treated with two different BPs over different periods, firstly with alendronate, and then with clodronate. The mandible was affected more frequently (61, 70.1%) than the maxilla (23, 26.4%), and three patients (3.5%) presented multiple BRONJ events.

The most frequent sign at presentation was bone exposure (82.8%), generally associated with pain and suppuration. BRONJ was defined and classified according to AAOMS [46], as follows: 15 patients with stage 0 (17.2%), 12 patients with stage 1 (13.8%), 53 patients with stage 2 (60.9%) and 7 patients with stage 3 (8.1%). The duration of bisphosphonate therapy at presentation ranged from 2 to 200 months (mean time ± standard deviation 44.9 ± 35.5 months; median 38 months, interquartile range = 20–60 months): 45 (51.7%) were BRONJ patients in treatment for ≤38 months. Dento-alveolar surgery, such as tooth extraction (due to dental/periodontal diseases), was the most common triggering factor for BRONJ (57/87 patients; 65.5%); two cases occurred in patients with ill-fitting dentures (2.3%) and other two cases occurred in patients with periodontal chronic disease and abscess (2.3%).

BRONJ localization was significantly associated only with age ($p = 0.002$): for people over 72 yrs of age, an increased risk of mandible localization with respect to maxilla (OR = 6.36, 95%CI = [1.89; 21.54]) (Table 3) was observed. None of the comorbidities and local risk factors for BRONJ were significantly associated with localization or stage at univariate analysis. At multivariate analysis, the increased risk of mandible localization with respect to maxilla for people older than 72 yrs (OR′ = 6.87, 95%CI = [2.13; 2.21]) was confirmed for a duration of administration >56 months (OR′ = 4.82, 95%CI = [2.13; 22.21]). The BRONJ stage was not associated with the duration of administration (Table 4).

Table 1
Demographical data and outcomes.

BRONJ observed patients	92	
Median age	72	
Q1–Q3	62–79	
BRONJ analyzed patients	87	
Median age	72	
Q1–Q3	61–79	
Mean age ± SD	70.7 ± 9.8	
	n(%)	
Gender		
Female	87(100)	
Male	0(0.0)	
Corticosteroid therapy	3(3.5)	
Comorbidities	Yes	No
	42(48.3)	45(51.7)
Diabetes	8(9.2)	
Hypertension	35(40.2)	
HCV-related liver diseases	1(1.2)	
Other cardiac	10(11.5)	
Type of administered BP		
Alendronate	77(88.5)	
Clodronate	7(8.1)	
Risedronate	2(2.1)	
Ibadronate	1(1.1)	
Site of BRONJ		
Mandible	61(70.1)	
Maxilla	23(26.4)	
Mandible and Maxilla	3(3.5)	
BRONJ stage according to AAOMS-update 2009		
Stage 0	15(17.2)	
Stage 1	12(13.8)	
Stage 2	53(60.9)	
Stage 3	7(8.1)	
Duration of bisphosphonate therapy at BRONJ presentation (months)		
Median duration	38	
Q1–Q3	20–60	
Precipitating event (local Risk factors for BRONJ)	Yes	No
	61(70.1)	26(29.9)
Tooth extraction	57(65.5)	
Periodontal chronic disease and abscess	2(2.3)	
Bone biopsy	0(0.0)	
Prosthetic trauma	2(2.3)	
Implantology	0(0.0)	

Table 2
Concomitance or not of systemic (S) and local (L) risk factors: number (%) of patients.

Concomitance of S and L	33(37.9)		
Presence of S alone	9(10.4)	Single 7(8.1)	Multiple 2(2.3)
Presence of L alone		Single 28(32.2)	Multiple 0(0.0)
No presence of S and/or L	17(19.5)		

4. Discussion

Bisphosphonates (BPs) are currently the main drugs for the prevention/treatment of osteoporosis: BP per os formulation is based on alendronate (the most widely prescribed), risendronate or ibandronate; i.m. injection with clodronate, and since 2006, i.v. therapy has been based on ibandronate, pamindronate or zoledronic acid. As a chronic disease, osteoporosis generally requires the long-term administration of BPs. Taking into account their benefits, BPs have been believed to conform to a safety profile in the treatment of osteoporosis [21]. Currently, women affected by osteoporosis, with a life expectancy of 83.4 yrs, may be treated in western countries (e.g. Italy) with BPs for many years [20], although a considerable controversy regarding the ideal duration of BP therapy exists [9,10,56].

Of the adverse effects of BPs, BRONJ has also been recognized in non-cancer patients affected by osteometabolic diseases [22,23,29,36,42,44,47,49], but always impacting less than expected in cancer patients. The real risk for patients in therapy with BPs for osteometabolic diseases developing BRONJ is not really known, in part due to the paucity of crucial information, such as the exact total number of patients exposed to BP, and to the precise interplay of the high number of suspected risk factors implicated (Table 5).

Concurring with other authors [11–13,32,41], we observed and described 87 cases of BRONJ in patients taking oral BPs; these cases have been described and correlated with other cases [5,12,16,31], mainly occurring in the mandible (73.6%). One limitation of our research was the non-controlled study design which may have led to an overestimation of BRONJ in non cancer-patients. There are very few RCTs dealing with this issue [1,8,18,19,28,39,51].

It is our opinion that BRONJ should be under the constant attention of all specialists who prescribe BPs for various reasons, be they to treat cancer or not, even if it is well known that i.v. BPs for cancer patients are more powerful than BPs for non-cancer patients (mainly per os). Furthermore, the reporting of BP off-label use can be described as

Table 3
Association between BRONJ localization and local and systemic risk factors: Odds ratios and 95%CIs.

Risk factors for BRONJ		Maxilla n = 23	Mandible n = 61	Mandible and Maxilla n = 3	p[a]
Age					
<72 yrs old	n(%)	18(78.3)	22(36.1)	2(66.7)	0.002
	OR	1.00	0.16	0.56	
	95%CI[b]		[0.05–0.53]	[0.04–7.93]	
≥72 yrs old	n(%)	5(21.7)	39(63.9)	1(33.3)	0.002
	OR	1.00	6.36	1.80	
	95%CI[b]		[1.89–21.54]	[0.13–25.70]	
Duration of administration					
≤24 months	n(%)	13(56.5)	17(22.9)	1(33.3)	0.050
	OR	1.00	0.30	0.38	
	95%CI[b]		[0.11–0.84]	[0.03–5.27]	
From 24 to 56 months	n(%)	6(26.1)	21(34.4)	0(0.0)	0.379
	OR	1.00	1.49	0 (0.0)	
	95%CI[b]		[0.50–4.38]	–	
>56 months	n(%)	4(17.4)	23(37.7)	2(66.7)	0.098
	OR	1.00	2.88	9.5	
	95%CI[b]		[0.84–9.80]	[0.53–171.48]	
Local risk factors					
Tooth extraction	n(%)	16(69.6)	39(63.9)	2(66.7)	0.889
	OR	1.00	0.78	0.88	
	95%CI[b]		[0.27–2.19]	[0.06–11.91]	
Spontaneous BRONJ	n(%)	5(21.7)	20(32.8)	1(33.3)	0.609
	OR	1.00	1.76	1.80	
	95%CI[b]		[0.56–5.49]	[0.13–25.70]	
Periodontal chronic disease and abscess	n(%)	1(4.4)	1(1.6)	0(0.0)	0.632
	OR	1.00	0.37	0 (0.0)	
	95%CI[b]		[0.02–6.28]	–	
Prosthetic trauma	n(%)	1(4.4)	1(1.6)	0(0.0)	0.632
	OR	1.00	0.37	0 (0.0)	
	95%CI[b]		[0.02–6.28]	–	
Comorbidity					
Absent	n(%)	14(60.9)	29(47.5)	2(66.7)	0.480
	OR	1.00	0.58	1.29	
	95%CI[b]		[0.22–4.62]	[0.10–10.41]	
Present	n(%)	9(39.1)	32(52.5)	1(33.3)	0.480
	OR	1.00	1.72	0.78	
	95%CI[b]		[0.64–4.62]	[0.06–10.41]	
Type of BP					
Alendronate	n(%)	20(87.0)	54(88.5)	3(100.0)	0.801
	OR	1.00	1.16	–	
	95%CI[b]		[0.27–4.96]	–	
All others	n(%)	3(13.0)	7(11.5)	0(0.0)	0.801
	OR	1.00	0.86	–	
	95%CI[b]		[0.20–3.70]	–	

[a] p-Values of χ^2 test or Fisher's exact test, where appropriate.
[b] Default standard errors used for 95%CIs.

remarkable, with an observation of 5.4% BRONJ cases in our sample, as similarly reported by others [43]. Generally, it is known that the use of drugs for unapproved indications is common [14]: the absence of regulatory approval for treatment indication could mean that a drug should be useful but adverse drug events, which may be less predictable, must be taken in account. Our findings indicate that off-label prescription should also be cautiously considered for this category of drugs.

In agreement with Malden and Lopes [31], we observed that the 88.5% of BRONJ patients were in therapy with alendronate, currently the most prescribed drug for osteoporosis. Given the current scarcity of a database involving a large number of people, it is not possible to establish "true" risk factors, apart from age, gender, steroid, and type of BP [26]. Authors have described in the literature the concomitant presence of comorbidities and/or so called-trigger (local) factors [53] (e.g. tooth extraction due to dental/periodontal diseases and dental/periodontal diseases) in many cases of BRONJ, also in osteoporotic non-cancer patients, where the potency and quantity of NBP is lower. Nearly half (48.3%) of the patients in our study displayed the

Table 4
Association between BRONJ localization and BRONJ stage with local and systemic risk factors: odds ratios and 95%CIs, p-values.

Variables	BRONJ localization				BRONJ stage	
	Mandible vs maxilla		Mandible and maxilla vs maxilla			
	OR 95%CI	p	OR 95%CI	p	OR 95%CI	p
Duration of BP administration						
From 24 to 56 months	3.04 [0.85; 10.85]	0.086	0.00[a]	0.991	2.1 [0.72; 6.10]	0.174
>56 months	4.82 [1.21; 19.24]	0.026	6.77 [0.47; 95.04]	0.161	0.79 [0.30; 2.13]	0.649
Age						
>72 yrs old	6.87 [2.13; 22.21]	0.001	1.85 [0.13; 26.08]	0.647		

[a] 95%CI not calculable.

Table 5
Most relevant studies (>10 cases) of BRONJ in osteometabolic patients.

Authors (ref)	No.	Gender	Mean age [yrs] (range)	BP type (no.)	Mean time [months] of administration	Motivation for BP therapy (no.)	Patients taking corticosteroids	Comorbidities (no.)	Lesion site (no.)	Trigger event (no.)
Marx et al. [59]	30	30 F	64.8 (NA)	A (27) R (3)	67	Osteopenia (16) Osteoporosis (14)	NA	Rheumatoid arthritis (3)	Md (29) Mx (1)	Dental extraction (15) Spontaneous (15)
Yarom et al. [58]	11	11 F	69.7 (55–79)	A (11)	49	Osteoporosis (9)	1	Rheumatoid arthritis (2) Hypothyroidism (3)	Md (8) Mx (3)	Dental extraction (7) Dental implant (2) Dental trauma (2)
Favia et al. [16]	24	24 F	71.5 (53–83)	A (15) C (3) R (2) I (2) A + C (1) C + R (1)	20	Osteoporosis (9) Orthopedic surgery (2)	3	Diabetes (1) Cryoglobulimenia (1) Arterial hypertension (7)	Md (21) Mx (9)	Dental extraction (18) Dental implant (4) Periodontal disease (5) Apical lesion (1) Spontaneous (11)
Lazarovici et al. [60]	16	NA	NA	A (16)	67	Osteoporosis (16)	NA	NA	NA	NA
Otto et al. [4]	37	30 F 7 M	68.7 (46–88)	A (28) R (4) I (3) C (1) A + R (1)	57	Osteoporosis (37)	NA	NA	NA	NA
Manfredi et al. [32]	25	25 F	70.4 (65–85)	A (12) I (1) C (1) N (1) A + I (3) A + C (2) A + R (2)	NA	Osteoporosis (25)	9	Rheumatoid arthritis (4) Diabetes (4)	Md (16) Mx (9)	Dental extraction (16) Dental implant (2) Spontaneous (7)
Malden and Lopes [31]	11	9 F 2 M	69 (48–83)	A (16)	36	Osteoporosis (7)	4	Rheumatoid arthritis (4) Diabetes (1) Cardiac conditions (7) Respiratory conditions (2)	Md (8) Mx (3)	Dental extraction (7) Dental trauma (2) Spontaneous (2)
Diniz-Freitas et al. [12]	20	19 F 1 M	71.2 (53–82)	A (16) I (4)	66	Osteoporosis (17)	7	Rheumatoid arthritis (3) Diabetes (5) Arterial hypertension (12) Osteoarthritis (3) Hypothyroidism (2)	Md (16) Mx (6)	Dental extraction (15) Dental implant (2) Apical lesion (1) Spontaneous (6)
Present paper	87	87 F	70.7 (53–92)	A (77) R (2) I (1) C (7)	44.9	Osteoporosis (87)	3	Rheumatoid arthritis (3) Diabetes (8) Arterial hypertension (35) Cardiac conditions (10)	Md (64) Mx (26)	Dental extraction (57) Periodontal disease (2) pProsthetic trauma (2)

presence of at least one comorbidity; in 32.2% of patients at least one local risk factor was present; concomitant comorbidities and triggers were observed in 37.9% of patients. This point is very important and it should also be taken into account in relation to BRONJ prognosis. O'Ryan and Lo [40] have recently observed that BRONJ patients taking oral BPs and with relevant comorbidities demonstrated a lower probability of healing and a longer median time in healing than patients without comorbidities.

On the other hand, we also wish to underline the observation in almost 20% (17/87) of "true spontaneous" BRONJ, whereby it was not possible to detect any potential systemic risk factors, comorbidities or local risk factors. This datum is of great interest to researchers and it could mean that BRONJ may occur without known risk factors. Moreover, it would be interesting to identify further risk factors hitherto unknown. Noteworthy is our opinion that the expression spontaneous BRONJ has been used incorrectly in the literature [40] since it is often being employed in cases of BRONJ unrelated to a surgical procedure (e.g. extraction due to dental/periodontal disease), but without specifying the presence or not of comorbidities or other trigger mechanisms.

The drug dose and the cumulative dose play a role in the initiation of necrosis, as well as the specific type of BP used [4]. Even if the longer-term use of oral BPs should have a dose equivalence effect [48], it is notable that the mean time of presentation was approximately 3 yrs (38 months) in the patients in this study, as already described in the literature [12,16,35]. Such a fact would indicate that the short time period of BP exposure may not always necessarily constitute a safety threshold relating to the risk of BRONJ in any given patient and, in every case, the tailoring of BP therapy to individual patients would be beneficial. The most frequent observation in our sample of the AAOMS stage 2 BRONJ (60.9%) correlates with the data reported in other studies [5,12,16,31]. It is our opinion that this frequent datum is relevant to explaining the incidence of a tardy BRONJ diagnosis, either due to delay, a misdiagnosis or a low level of awareness by the physician.

A primary goal should be to preserve or to obtain the status of good oral health, regardless of the duration of BP treatment. According to the European Medicines Agency (EMEA)[15], a dental examination is advised in non-cancer patients prior to commencing BP therapy, only if the dental status has been evaluated as poor. Paradoxically, the manner of evaluating dental status is not specified by the EMEA. In this regard, the Italian Society of Oral Medicine and Pathology has published an online questionnaire with the aim of

helping the practitioner to establish if the patient's dental status is poor and if s/he requires a specialist dental examination (http://www.sipmo.it/), as advised by the EMEA.

According to Loukota [30], the BRONJ phenomenon is growing exponentially and we believe that the requisite of preventing local risk factors (e.g. tooth extraction to dental/periodontal diseases and dental/periodontal diseases) is unquestionable, also when BP should be prescribed for non-cancer indications. Recently, other Italian authors [2] have underlined the necessity of increasing the knowledge and adequate reporting of the BRONJ phenomena by health professionals, and of improving the elaboration of effective BRONJ preventive protocols [52], in order to minimize as far as possible the severe adverse effects of such an efficacious medical treatment.

In conclusion, it is our opinion that the administration of oral BP, particularly in excess of 2.5–3 yrs, should be responsibly considered. The relevance of this is that the serious adverse effects associated with oral BP (such as BRONJ and atypical femur fracture) are still being reported (and not so infrequently). In this scenario, cumulative BP-doses will hopefully be tailored to patients' needs and consequently a higher degree of general safety attained. Another strategy, also concomitantly, should be to reach and to maintain good oral health, by means of adequate protocols of primary and secondary prevention, especially for prolonged BP therapies in individuals with comorbidities.

Learning points

- All authors consider essential the observation of all patients before and in therapy with bisphosphonates (cancer and not) since in literature many reports of BRONJ (Bisphosphonate related osteonecrosis of the jaws) in osteoporotic patients are present.
- The application of prevention protocols also in osteoporotic patients could reduce the risk of BRONJ.
- Also in absence of known risk factors, the spontaneous BRONJ is almost 20% in our sample: it could mean that it is essential to proceed with the identification of further risk factors hitherto unknown.

Conflict of interest

All of the authors have no financial interest or other relationships in the material.

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