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Multiple myeloma vs. breast cancer patients with bisphosphonates-related osteonecrosis of the jaws: a comparative analysis of response to treatment and predictors of outcome

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BACKGROUND: Multiple myeloma (MM) and breast cancer (BC) are the two most common diseases associated with bisphosphonates-related osteonecrosis of the jaws (BRONJ), for which different therapeutical approaches have been proposed. The aim of this study was to compare the clinical behaviour of BRONJ in patients with MM vs. BC and the time of healing in terms of clinical and symptomatological remission, following a standardized therapeutic protocol.

METHODS: Twenty-six BRONJ patients (13 men with MM and 13 women with BC) were prospectively enroled and treated with a specific systemic and topical antibiotic therapy. Several predictors of outcome were also evaluated.

RESULTS: Nine patients (69.2%) with BC and 10 patients (76.9%) with MM progressed towards a complete clinical remission (CR) in a mean healing time of 183.3 days [SD: 113.7; 95% confidence interval (CI): 95.95–207.7] and 372.0 days (SD: 308.0; 95% CI: 151.7–592.3) ($P = 0.776$), respectively. The clinical improvement was statistically significant ($P = 0.0013$ and $P = 0.0014$), as well as the assessment of pain ($P = 0.0015$ and $P = 0.0015$), in MM and BC group, respectively. Cox regression analysis revealed that just triggering events ($P = 0.036$) were found to be significant predictors of outcome of BRONJ healing.

CONCLUSIONS: Both groups of cancer patients experienced clinical and symptomatological remission regardless their malignancy, but BC patients earlier than MM patients.

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Introduction

Bisphosphonates-related osteonecrosis of the jaws (BRONJ) is a new pathological condition, characterized by the exposure of maxillary and/or mandibular necrotic bone, following the administration of a drug belonging to the category of bisphosphonates (BPs) (1–3).

By consensus, BRONJ is defined as exposed bone in the maxillofacial region that had persisted more than 6 (4) or 8 weeks (5) in patients treated or in treatment with BP, without evidence of local metastasis and/or administration of radiotherapy to the upper and/or lower jaw.

The majority of BRONJ cases were reported to be induced by intravenous BP, nonetheless even oral BPs may provoke BRONJ (6, 7), although with a lower risk (8).

Several position papers (5, 9–12) have attempted to set a unanimously accepted definition, classification, diagnostic criteria and treatment of BRONJ, and write universal preventive guidelines, trying to provide more information about epidemiology, aetiology, pathophysiology and risk factors, but the topic still remains elusive and highly debated in the literature, mostly in the light of an increasing evidence of the non-exposed variant of BRONJ (stage 0) (13). BRONJ patients are now classified into four different stages: (i) stage 0 a/s (asymptomatic/symptomatic), (ii) stage 1, (iii) stage 2 and (iv) stage 3 (5, 10).

Currently, no universal and standardized therapeutic protocol has been approved for treating BRONJ, but just several guidelines, that commonly suggest a

conservative approach (14). It is not yet clear whether or not the discontinuation of BPs may provide an improvement of osteonecrosis of the jaw (ONJ). Conversely, a radical surgical approach seems to be too aggressive or better contraindicated, as some relapse have been described up to 14 months after surgery (15).

The primary end-point of this study was to compare the clinical behaviour of BRONJ in patients with multiple myeloma (MM) vs. breast cancer (BC) and the time of healing in terms of clinical (no evidence of bone exposed in the oral cavity) and symptomatological remission (no pain), following a combined systemic and topical antibiotic therapeutical algorithm. The secondary end-point was to assess whether and which of the below-stated variables (see Study variables, Materials and methods) might have played a role as a possible predictors of outcome of BRONJ healing in both groups, thus fostering its possible amelioration or worsening.

Materials and methods

Study design

This investigation was a single-centre prospective open-label clinical trial, carried out between January 2006 and December 2009, at the Oral Medicine Unit, Federico II University of Naples, Italy. All patients provided their written informed consent before participating into the study. The study was conducted in accordance with the ethical principles provided by the Declaration of Helsinki and the principles of good clinical practice. Study design, inclusion and exclusion criteria and treatment protocol were reviewed and approved by a council of senior specialists at the same Department of our University.

Patients were recruited if they met the following inclusion criteria:

1 patients with diagnosis of BRONJ in stage 2 or 3 (5), confirmed by biopsy and radiological exams [orthopantomography (OPT) and bi- and tridimensional computed tomography (CT) scan];
2 males patients with MM who received the same/similar therapeutic protocol (e.g., corticosteroids and/or chemotherapy and/or hormonal and/or inhibitor of angiogenesis) for their specific underlying malignancy prior to the onset of BRONJ;
3 women with BC who received the same/similar therapeutic protocol (e.g., corticosteroids and/or chemotherapy and/or hormonal and/or inhibitor of angiogenesis) for their specific underlying malignancy prior to the onset of BRONJ;
4 MM and BC patients who received zolendronic acid (ZA) intravenously only, one dose per month, for at least 6 months;
5 MM and BC patients who discontinued BP therapy after BRONJ onset;
6 patients who received the established antibiotic protocol of the study only;
7 no history of radiotherapy in the oro-maxillofacial region;
8 no evidence of jawbone metastases;
9 6 months minimum of follow-up (range 6–12 months).

Study variables

In both groups A and B, we evaluated three parameters: clinical, radiological and symptomatological (pain) features prior to and after the treatment. Complete remission (CR) was defined as the total absence of clinical signs (no evidence of bone exposed in the oral cavity, erythema, purulent discharge, swelling) and symptoms (no pain). The presence of symptoms was evaluated measuring pain via a '11-numerical rating scale' (11-NRS) (16).

We also considered 11 further variables, as predictors of outcome, chosen based on the current knowledge of BRONJ pathophysiology: age, sex, type of cancer, site of BRONJ (mandible, maxilla, mandible and maxilla), extent of BRONJ, stage at admission, concurrent systemic diseases, smoke, triggering events (dental extraction, periodontal disease, dental prosthesis, implants), major surgical therapy (Table 1) and exposure time to BP (number of BP cycles) (Table 2).

Extent of BRONJ was defined as the size of necrotic bone involving upper and/or lower jaw. It was considered mild if bone involvement ranged from 1 to 3 cm, moderate from 4 to 6 cm, and severe more than 6 cm.

Therapeutic protocol

All patients in stage 2 or 3 were treated initially with Subactam/Ampicillin (500 mg + 1 g/3.2 ml bid IM) for 10 days, then received Amoxicillin/Clavulanate (500 mg tid PO), Chlorexidine 0.2% as mouthwash three times a day, and hydrogen peroxide 10 volumes diluted 1:1 with water to be used as mouthwash three times a day. Therapy was scheduled permanently until a remission of symptomatology, and stop of progression of the disease was achieved.

Pain was treated with three different painkiller drugs: ketorolac (30 mg bid IM) for 2 days in case of severe and unbearable pain, then Nimesulide (100 mg bid PO) or Acethaminophen (1000 mg tid PO).

In a few cases, sequestrectomy was performed without no decortications or debridement of bed and/or margin of the remaining lesion to foster a safe closure of soft tissues.

Follow-up

Haematological parameters and radiological examinations (OPT, bi- and tridimensional CT scan) were performed every 2 months. The time of follow-up was calculated starting as soon as patients had reached CR or stage 1.

Statistics

The independent variables were checked for normal distribution via the Shapiro–Wilk normality test. The comparison of variables between group A and B was evaluated via a two-tailed *t*-test, if they met the normality assumption; conversely those variables that did not meet the normality assumption were evaluated

Table 1 Characteristics of breast cancer and multiple myeloma patients at the time of diagnosis of bisphosphonates-related osteonecrosis of the jaws (BRONJ)

	Multiple myeloma		*Breast cancer*		
Characteristics	*No. of patients*	*%*	*No. of patients*	*%*	P
Age (years)					
Range	59–76	49–79			0.093
Median	70	63			
Mean	68.4	63.1			
SD	4.85	9.85			
SE	1.34	2.63			
CI 95% interval	65.45–71.32	57.33–71.32			
Location of BRONJ					
Maxilla	5	38.5	4	30.8	0.824
Mandible	6	46.1	7	53.8	
Maxilla and mandible	2	15.4	2	15.4	
Radiological findings					
Lytic bone lesions	13	100	13	100	0.792
High bone density/Thickening periostium	13	100	13	100	
Fracture	3	23	3	23	
Clinical findings					
Inflammation	13	100	13	100	0.906
Pain	13	100	13	100	
Oral antral/nasal communication	1	7.7	0	0	
Extraoral fistulas	5	38.5	6	46.1	
Abscess	13	100	13	100	
Extent of BRONJ					
Mild	6	46.2	10	77	0.075
Moderate	4	30.8	3	23	
Severe	3	23	0	0	
Concurrent systemic diseases					
Hypertension	3	23	6	46.1	0.121
Osteoporosis	0	0	8	61.5	
Diabetes	1	7.7	3	23	
Triggering events					
Dental extraction	9	69.2	11	84.6	0.768
Periodontal disease	2	15.4	2	15.4	
Dental prosthesis	1	7.7	0	0	
Implants	1	7.7	0	0	
Major surgery	2	15.4	2	15.4	0.967
Smoking habit	2	15.4	3	23	0.652

Table 2 Comparison of stage, pain (11-NRS), extent of BRONJ prior to and after therapy, and time of exposure to BP (time from initial infusion to the last infusion prior to develop BRONJ) in multiple myeloma vs. breast cancer patients. This was expressed by number of cycles, which was equivalent to the number of months, as each cycle of ZA was performed once a month

	Group	*Mean*	*SD*	*95% CI*	*SE*	*P*
Stage prior to	MM	2.61	0.50	2.30–2.92	0.14	0.975
	BC	2.61	0.50	2.30–2.92	0.14	
Stage post	MM	0.23	0.43	−0.03–0.49	0.12	0.689
	BC	0.30	0.48	0.01–0.59	0.13	
Pain prior to	MM	8.00	1.35	7.18–8.81	0.37	0.789
	BC	7.84	1.21	7.11–8.58	0.33	
Pain post	MM	0.84	0.80	0.36–1.33	0.22	0.724
	BC	1.07	1.11	0.40–1.75	0.30	
BP cycles	MM	21.77	11.21	15–28.54	3.10	0.626
	BC	24.92	13.16	17–32.87	3.65	

BRONJ, bisphosphonates-related osteonecrosis of the jaws; MM, multiple myeloma; BC, breast cancer; SD, standard deviation; CI, confidence interval; SE, standard error; BP, bisphosphonates; ZA, zolendronic acid.

via the Mann–Whitney *U*-test. The comparison of independent variables within the same group was evaluated via the Wilcoxon signed-rank test.

Development of CR in patients with BC and MM receiving ZA treatment was set as the outcome variable (dependent variable). The Kaplan–Meier method was used to estimate the probability that a BC and MM patient will reach CR after treatment, i.e., time to reach a complete clinical remission in days. In addition, survival analysis was used to estimate the cumulative hazard of developing BRONJ in stage 3 vs. 2, comparing the two groups; time of exposure to BP

expressed in cycles was used as the primary time variable.

The effect of candidate predictors of outcome for BRONJ healing was measured using multivariate Cox proportional hazards regression analysis. The selection of covariates introduced in the model has been performed with a forward stepwise procedure based on likelihood ratio. Variables that were significant at $P < 0.10$ were considered in the Cox proportional hazards regression model. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) are reported.

P-values of <0.05 were considered significant and performed using the SPSS software (SPSS for Windows, version 17.0; SPSS Inc, Chicago, IL, USA).

Results

Patients' characteristics

The general patients' characteristics of 26 cancer patients (13 men with MM and 13 women with BC) who developed BRONJ are summarized in Table 1.

All patients underwent a bone and oral mucosal biopsy and none of them showed the presence of mucosal and/or bone metastasis. Histopathological examination revealed the presence of necrotic bone, confirming the diagnosis.

At admission, in both groups eight patients (61.6%) were in stage 3 and 5 patients (38.4%) were in stage 2, with variable symptoms. All patients presented with abscess and pain, accompanied by swelling and inflammation, five men and six women presented with purulent discharge and extraoral fistula, while just one man with oro–antral communication.

At the time of BRONJ onset, all patients completed the planned BP therapy and were in remission as regards their underlying malignancy. So, none of them discontinued BP therapy because of BRONJ.

After reaching stage 1, because of a wide exposure of the bone, two patients per group underwent major surgery: one received an emi-maxillectomy and three received an emi-mandibolectomy. Two patients smoked 20 cigarettes per day, while three patients smoked <10. No patient was alcohol or drug-addicted. Concurrent underlying systemic diseases and triggering events are summarized in Table 1.

No statistical differences were seen in all examined independent variables (Table 1), as well as in stage at admission (MM vs. BC, $P = 0.975$), pain prior to therapy (MM vs. BC, $P = 0.789$) and number of BP cycles (Table 2). Indeed, the duration of BP therapy (time of exposure) ranged in both groups from 6 to 48 cycles with a median number of 24 cycles ($P = 0.626$) (Table 2).

As all examined variables did not meet the criteria of normality assumption, they were evaluated via the Mann–Whitney *U*-test.

Therapeutic outcome

A complete clinical and symptomatological resolution of BRONJ was accomplished in about 70% of BC patients and 77% of MM patients. The outcome of therapy was clinically and statistically significant, in terms of stage (MM $P = 0.0013$ and BC $P = 0.0014$) and pain (MM $P = 0.0015$ and BC $P = 0.0015$) (Wilcoxon signed-rank test $P < 0.05$) (Table 3). Indeed, 13 of 16 patients in stage 3 reached CR and three patients in stage 1, whereas six of 10 patients in stage 2 reached CR and four patients in stage 1. None of them reported any adverse events related to the chronic systemic antibiotic therapy.

Table 3 Comparison of stage and pain (11-NRS) prior to and after therapy in each single group of patients

Group	*Mean*	*SD*	*95% CI*	*SE*	P
MM					
Stage prior to	2.61	0.50	2.30–2.92	0.14	0.0013
Stage post	0.23	0.43	−0.03–0.49	0.12	
Pain prior to	8.00	1.35	7.18–8.81	0.37	0.0015
Pain post	0.84	0.80	0.36–1.33	0.22	
BC					
Stage prior to	2.61	0.50	2.30–2.92	0.50	0.0014
Stage post	0.30	0.48	0.01–0.60	0.13	
Pain prior to	7.84	1.21	7.11–8.58	0.33	0.0015
Pain post	1.07	1.11	0.40–1.75	0.30	

BRONJ, bisphosphonates-related osteonecrosis of the jaws; MM, multiple myeloma; BC, breast cancer; SD, standard deviation; CI, confidence interval; SE, standard error; BP, bisphosphonates.

Kaplan–Meyer survival curve (Fig. 1) showed that there was no statistical difference between the two groups in terms of course of clinical remission ($P = 0.776$). Indeed, nine BC patients (69.2%) progressed towards CR in mean of 183.3 days (SD: 113.7; 95% CI: 95.95–207.7) vs. 10 MM patients (76.9%), who experienced CR in a longer time, that was a mean of 372 days (SD: 308; 95% CI: 151.7–592.3). The overall mean rate of CR considering all 19 patients was 284.2 days (SD: 249; 95% CI: 172.2–396.2).

The mean time of follow-up for the cohort of BC patients was 10.15 months (SD: 4.75; 95% CI: 7.27–13.03) (range 6–24; median: 9) and of MM 10.54 (SD:

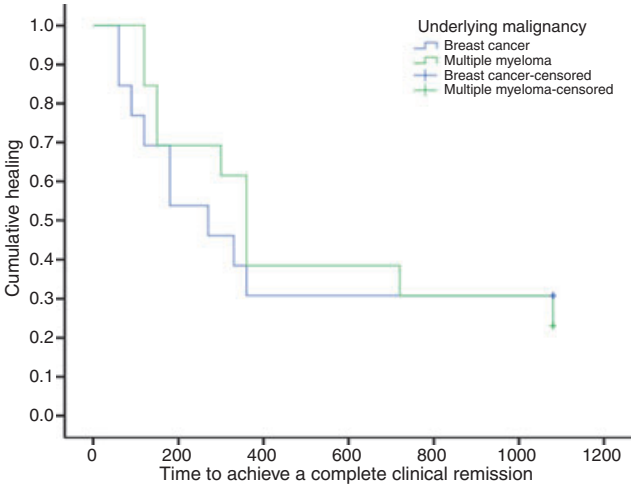

Figure 1 Kaplan–Meier estimate of the time to achieve complete clinical remission in multiple myeloma vs. breast cancer patients.

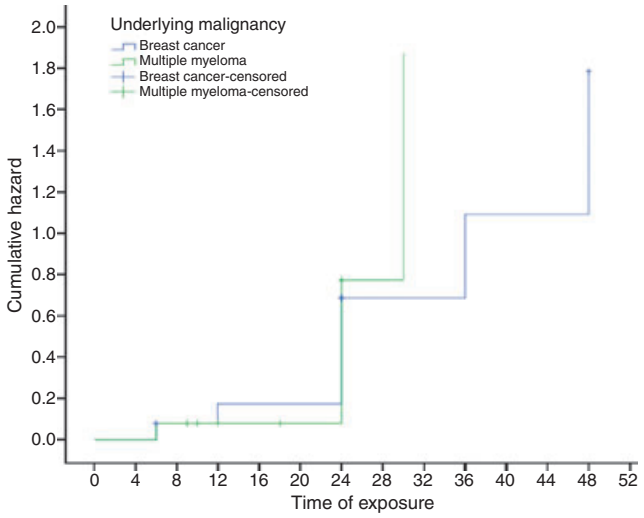

Figure 2 Cumulative hazard of developing bisphosphonates-related osteonecrosis of the jaws in stage 3 vs. stage 2 from the date of initiation of treatment in multiple myeloma and breast cancer patients.

5.31; 95% CI: 7.32–13.75) (range: 6–20; median: 8) during which only two BC patients died because of complications directly related to their underlying malignancy and not to BRONJ or the instituted treatment. No patient in CR developed any recurrence for the entire period of follow-up. Sequestrectomy was accomplished in four (15.3%) of 26 patients.

Eventually, comparison of final stage ($P = 0.689$) and pain after therapy ($P = 0.724$) between MM and BC patients did not show any statistically significant difference (Table 2).

Predictors of outcome for BRONJ healing

The cumulative hazard of developing BRONJ in stage 3 vs. stage 2 did not show any significant statistical difference comparing the survival curves of the two groups ($P = 0.522$). Indeed, the cumulative hazard of developing stage 3 increased up to 77.3% (95% CI: 26.6–201.2) and 68.6% (95% CI: 24.0–151.1) in MM and BC group, respectively, after 24 cycles (months) of therapy (Fig. 2).

The predictors of outcome not included in the model were as follows: cancer ($P = 0.783$), gender ($P = 0.783$), extent of BRONJ ($P = 0.514$), site per extent of BRONJ ($P = 0.429$), time of BP exposure per extent of BRONJ ($P = 0.575$), Stage at admission ($P = 0.896$), Concurrent systemic disease ($P = 0.139$), Smoking habit ($P = 0.869$), Major surgery ($P = 0.505$). The number of cycles and site of bone involved were evaluated in relation to the extent of the disease. The results of Cox proportional hazards regression analysis revealed that, in both groups, just triggering events ($P = 0.036$) turned out to be statistically significant, while age was no longer a statistically significant covariate ($P = 0.071$; HR: 0.947; 95% CI: 0.893–1.005). This analysis showed that the rate of healing in cancer patients who developed BRONJ following periodontal disease ($P = 0.031$; HR: 3.891; 95% CI: 1.131–13.388), and very marginally following implants ($P = 0.066$; HR: 8.278; 95% CI: 0.867–79.31), has a higher rate of healing than those who underwent dental extractions.

Discussion

The general characteristics of our study groups (Table 1) showed that the age of BRONJ onset is a little bit higher in MM than BC group, but this could be because of the variable nature of the underlying disease, rather than an observation related to BRONJ. Also, the presence of trauma (dental extractions), as triggering event, has shown a higher prevalence than the others, in line with a previous report (3). As the number of cycles was quite homogeneous (range: 6–48) in both groups and the site was just indicative of the BRONJ location and not representative of any objective measure, both these predictors were analysed in relation to the extent of the disease. Also, we decided to recruit patients who received only ZA, as this BP showed the highest incidence of BRONJ, after a very short administration (one cycle per month for 12–18 months) (9).

Our study appears to be the first reporting a comparison between MM and BC patients with BRONJ, in terms of time of attainment a stable clinical remission. Commonly, in the literature, these groups were analysed separately. MM patients turned out to be more affected than BC patients (9.9% vs. 2.9%, respectively), and BP exposure and the type of BP were the two most important risk factors (17). Indeed, patients treated with only ZA were at higher risk (21% after 3 years of BP exposure) of developing BRONJ than those ones treated with both ZA and Pamidronate (PAM) (7% after 4 years of BP exposure), due to probably a more potent inhibitory effect of ZA on bone turnover (18). Further studies analysed several risk factors for developing BRONJ: some of them (2, 18) confirmed that dental extraction represented the most important risk factors in either MM (18) or BC (2) patients, and in addition that in MM patients even age seems to be an important risk factors (18).

Our results confirmed that dental extractions, as triggering events, represent an important predictor of outcomes, and also it appears that patients with BRONJ because of periodontal disease have a higher rate of healing than those ones who underwent dental extraction. Nevertheless, a wider sample of patients is needed to confirm these data. How a traumatic injury might play a role in delaying BRONJ healing remains an open question. Conversely, another study (19) has shown that MM patients with spontaneous, unprovoked BRONJ are at higher risk of recurrence and non-healing lesions, and, intriguingly, MM relapses were more common in patients with recurrent/non-healing BRONJ lesions. It is unclear whether this last depended on the type of cancer or different therapeutic protocols adopted in the study. Whether the underlying malignancy is able solely to influence the clinical course of BRONJ still remains unknown. It appears that in MM patients there would be an increasing trend of developing BRONJ from 1.9% in 2002–2005 to 3.6% in 2006–2008 (20), with a very low

rate of healing (41%). Unfortunately, it is not clear what were the type of medical treatment and the covariates of the study group that might have influenced the clinical course of BRONJ.

The statistical analysis of our results showed that both groups were quite homogenous either before or after receiving the therapeutic protocol (Tables 1 and 2) and responded satisfactorily to the therapeutic protocol regardless their underlying malignancy in terms of pain (Table 3).

Although the overall mean rate of the time for reaching a CR in BC patients was 191.7 days less than in MM patients, such difference was clinically relevant, but not considered statistically significant ($P = 0.757$; log-rank test result on Kaplan–Meier survival comparison), as either BC or MM group was capable to enter in remission with such therapy in a variable period of time, despite the difference between the underlying malignancy. Indeed, 77% of MM patients healed, in line with a previous study (19), and 70% of BC patients. The reason because of what MM and BC groups experienced this clinical difference, although not statistically significant, in terms of reaching CR (372 vs. 183.3 days, respectively) remains to be elucidated. However, we may hypothesize that the presence of an underlying concurrent immunodeficiency in MM group might have played a role.

Even though the therapy did not allow all cancer patients to reach CR, nonetheless the achievement of stage 1 for four BC and three MM patients was considered an acceptable outcome in terms of stabilized disease and improvement of their quality of life.

From the analysis of the overall variables examined by a regression model, just triggering events, and marginally age controlling for all other variables in the model, were statistically significant, unlike a previous study (3) that reported exposure of BP, cancer therapy and stage at admission, as predictors of outcome. It is likely that these differences were probably determined by the fact such patients' groups were not homogeneous in terms of underlying disease (five different types of cancer: more than 50% with BC) and number of cycles, with a very wide range (4–115) (3).

We have tried to eliminate these biases, making as more homogenous as possible both groups and setting very stringent inclusion criteria. This led some limitations: a small group of patients and the absence of a control group (patients in stage 2 or 3) that would have been ethically unacceptable to treat with placebo, though. Another limitation was to not have men with BC and women with MM and, so, this did not allow us to draw any final conclusion between sex and development of BRONJ. Similarly, it would be important and interesting to perform the same investigation on other types of cancer, for example women and men with lung, kidney or brain cancer, to better ascertain whether sex and underlying malignancy might influence the course of therapy. How the difference of an underlying malignancy, sex and therapy for controlling cancer may have influenced the time of BRONJ onset still remains an open question, warranting further investigations. Lastly, but no less important, two further biases might have occurred: any surgical biopsy performed in all patients to confirm BRONJ might have affected or worsened their prognosis and the absence of BRONJ patients in stage 1.

Recently, seven different therapeutic protocols have been proposed (21), and it appears that the best was cessation of BP for more than 6 months, hyperbaric oxygen therapy, surgery and long-term antibiotic therapy. However, these favourable results were only obtained in seven of 60 patients of which just two with MM and two with BC, treated with different BPs. Considering the non-homogenous BP therapy received by patients, it seems difficult to ascertain the real validity of this therapeutic protocol.

In conclusion, both BC and MM patients experienced clinical and symptomatological remission in different times, regardless their underlying oncological disease. Despite our encouraging results about our therapeutical approach, the treatment of BRONJ patients still remains a big challenge and, thus, randomized controlled clinical trials on wider samples of matched patients are warranted.

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