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ORIGINAL ARTICLE

# Evolution of bisphosphonate-related osteonecrosis of the jaw in patients with multiple myeloma and Waldenstrom's macroglobulinemia: a retrospective multicentric study

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Bisphosphonates (BPs) are used intravenously to treat cancer-related conditions for the prevention of pathological fractures. Osteonecrosis of the jaw (BRONJ) is a rare complication reported in 4–15% of patients. We studied, retrospectively, 55 patients with multiple myeloma or Waldenstrom's macroglobulinemia followed up from different haematological departments who developed BRONJ. All patients were treated with BPs for bone lesions and/or fractures. The most common trigger for BRONJ was dental alveolar surgery. After a median observation of 26 months, no death caused by BRONJ complication was reported. In all, 51 patients were treated with antibiotic therapy, and in 6 patients, this was performed in association with surgical debridement of necrotic bone, in 16 with hyperbaric $O_2$ therapy/ozonotherapy and curettage and in 12 with sequestrectomy and $O_2$/hyperbaric therapy. Complete response was observed in 20 cases, partial response in 21, unchanged in 9 and worsening in 3. The association of surgical treatment with antibiotic therapy seems to be more effective in eradicating the necrotic bone than antibiotic treatment alone. $O_2$ hyperbaric/ozonotherapy is a very effective treatment. The cumulative dosage of BPs is important for the evolution of BRONJ. Because the most common trigger for BRONJ was dental extractions, all patients, before BP treatment, must achieve an optimal periodontal health.

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## INTRODUCTION

Bisphosphonates (BPs) have been mainly used in onco-haematology for the treatment of patients with solid tumour and bone metastasis such as lung, breast and prostate cancer.[1,2] They are also prescribed for patients with hypercalcaemia, multiple myeloma (MM), Waldenstrom's macroglobulinemia (WM), as well as for osteoporosis and Paget's disease.[3–6] Among the different BPs, the most widely used BPs in oncology and haematology are pamidronate and zoledronic acid.[7] At the cell level, BPs act by blocking osteoclast function in several ways: inhibiting the osteoclast formation from monocytes,[8] reducing osteoclasts' life cycle[9] and inhibiting the osteoclastic activity on the bone surface.[10] At the molecular level, BPs are deemed to modulate osteoclast function, interacting with a surface cell receptor or with an intracellular enzyme.[11] Considering that they are not metabolised for long, they are internalized in the osteoclasts, causing their death (osteoclast apoptosis).[12] In addition to the anti-reabsorption effect on the bone, an anti-angiogenetic effect on animals has been recently described.[13] BPs can inhibit the endothelial cell function both *in vivo* and *in vitro*.[14] The cells treated with BPs have shown a decreased proliferation capability, an increased apoptosis degree and a reduced capillary vessel formation.[15,16] Other effects are immunomodulating and antineoplastic.[17,18] As adverse effects, BP treatment produces flu-like symptoms, fatigue, gastrointestinal disorders, anaemia, dyspnoea and oedemas.[19] Oral and oesophageal mucosal ulcerations were also observed.[20,21] In 2003, following the clinical observations by Marx and Stern,[22] a possible implication of BPs in the development of maxillary osteonecrosis was postulated. Later, this hypothesis was also supported by several authors who highlighted a strong correlation between intra-oral bone necrosis and BP treatment, especially after tooth avulsion or other oral cavity surgeries.[23–26] This problem has been described in neoplastic and non-neoplastic diseases during long-term treatment with BPs with an incidence between 4 and 15% as reported in different papers.[24] The most common clinical finding is an area of ulcerated mucosa and an exposed devitalized bone.[27] The exposed bone surface is irregular, and the surrounding soft tissue is often inflamed for secondary mucosal infection and is painful.[28–30]

The treatment objectives for patients with BP-related osteonecrosis of the jaw (BRONJ) are to eliminate pain, control infection of the soft and hard tissue, minimize the progression of bone necrosis and eliminate exposed bone.[19]

The aim of this retrospective multicentric study is to describe the clinical aspects and the evolution of the osteonecrotic lesions in MM and WM patients treated with BPs and followed up for more than 6 years.

## PATIENTS AND METHODS

We studied retrospectively 55 patients with MM or WM followed up at 10 haematological departments of our region from January 2003 to January 2009. Radiological investigations and biopsies were performed to confirm clinical diagnosis of BRONJ. Clinical diagnosis was based on the following criteria: exposed or necrotic bone of maxilla or mandible with or without pain, evidence of regional soft-tissue inflammatory swelling or infection,

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**Table 1.** Characteristics of the population studied

| | |
|---|---|
| *Patients 55* | |
| 16 Males; 39 females | |
| Median age 72 years (range 56–95) | |
| *Immunoglobulin isotype* | |
| IgG-k | 25 patients |
| IgG-λ | 6 patients |
| IgA-k | 12 patients |
| IgA-λ | 3 patients |
| MM-k | 3 patients |
| MM-λ | 1 patient |
| WM IgM-k | 5 patients |
| *Type of Bisphosphonate used* | |
| Pamidronate | 1 patient (1.8%) |
| Zoledronic acid | 36 patients (65.5%) |
| Pamidronate/Zoledronic acid | 18 patients (32.7%) |
| *Mean cumulative dose* | |
| Pamidronate | 2.022 mg (range 90–6.750 mg) |
| Zoledronic acid | 84 mg (range 4–256 mg) |

**Table 2.** Site and trigger of ONJ

| | |
|---|---|
| *SITE of ONJ* | |
| Mandible | 29 patients (52.7%) |
| Mandible and maxilla | 4 patients (7.3%) |
| Maxilla | 22 patients (40%) |
| *Trigger for ONJ* | |
| Dentoalveolar surgery (including extractions) | 43 patients (78.4%) |
| Dental implant placement | 3 patients (5.4%) |
| Periodontal disease | 5 patients (9%) |
| Dental prothesis | 3 patients (5.4%) |
| No trigger | 1 patient (1.8%) |

exposed bone with pathological fracture with pain, swelling or cutaneous fistula. All patients, but two, were on chemotherapy; none of them was previously irradiated in the head and neck region or had evidence of MM bone disease in the jaw. Patients characteristics are summarized in Table 1; the female/male ratio $>2$ is noteworthy.

Anatomic localization of the BRONJ was as follows: mandible in 29 patients (52.7%), maxilla in 22 patients (40%) and mandible and maxilla in 4 cases (7.3%). The most common trigger for BRONJ was dental-alveolar surgery, including extractions (43 patients, 78.4%), dental implant placement (3 patients, 5.4%), periodontal disease (5 patients, 9%) and dental prosthesis (3 patients, 5.4%); apparently, only 1 patient (1.8%) developed BRONJ spontaneously (Table 2). The staging of BRONJ according to the algorithm described by Ruggiero *et al.*[19] was as follows: 4/55 patients (7.3%) had stage 1 BRONJ, 46 patients (83.8%) had stage 2 BRONJ and 5 patients (9%) had stage 3 BRONJ. Once BRONJ was diagnosed, all patients discontinued BP therapy. At the time of diagnosis, 12 patients were in remission of the haematological disease (according to the classification of the International Myeloma working group),[28] whereas the others were in disease plateau or progression.

According to the clinical BRONJ presentation, patients were treated with different approaches.

A group of patients received only antibiotic therapy, broad spectrum or more specific according to culture antibiogram, in association with local treatment with benzidamine (that is, quinolone or penicillin plus metronidazole). A second group received antibiotic therapy in association with local washes and surgical debridement of necrotic bone. Another group received antibiotic therapy, $O_2$ hyperbaric/ozonotherapy with or without surgical debridement and the last group underwent sequestrectomy (surgical removal of a fragment of dead bone that has separated from healthy tissue as a result of disease) or partial ostectomy. Ozonotherapy was performed as described from Petrucci *et al.*[6] Infact, hyperbaric $O_2$ therapy, by locally increasing the $O_2$ content of the blood, produces a significant reduction in the risk of wound infection.[31]

**Table 3.** Treatment and response

| | |
|---|---|
| *Type of treatment* | |
| Antibiotic only | 19 patients |
| Antibiotic+curettage | 6 patients |
| Antibiotic+hyperbaricO2/ Ozonotherapy+curettage | 16 patients |
| Antibiotic+hyperbaricO2/ Ozonotherapy+sequestrectomy | 12 patients |
| No treatment | 2 patients |
| *Overall response to treatment* | |
| Resolution | 20 patients (36.4%) |
| Improvement | 21 patients (38.2%) |
| No change | 9 patients (16%) |
| Progression | 3 patients (0.05%) |
| Not evaluable | 2 patients (3.6%) |

In 19 patients (34.5%), antibiotic therapy was the only treatment used. Two patients (4%) refused therapy. Six patients (11%) received antibiotic therapy in association with surgical debridement of necrotic bone. Sixteen patients (29.%) were treated with antibiotic therapy in combination with ozonotherapy and surgical debridement; 12 patients (22%) required sequestrectomy in association with antibiotic and $O_2$/hyperbaric therapy (Table 3).

### Statistical analysis

Statistical comparisons among subgroups were carried out using the Chi-squared test with Yates' correction for small numbers and Student's *t*-test as appropriate. A stepwise discriminant regression analysis was performed. The individually tested dependent variables included the following: cure and amelioration of BRONJ and other clinical data. Independent variables included sex, site of BRONJ, type of monoclonal gammopathy, type of BP used and eventually the sequence, total dosage of BP, type of treatment if medical, surgeon or both, with or without $O_2$ therapy. A cut-off for dosage of zoledronic acid was chosen at a total dose of 80, 100, 110, 120 and 130 mg, considering the distribution of the success rates at progressive values of these variables. The odds ratio and relative 95% confidence interval were also calculated. Differences were considered significant at a 5% probability level.

## RESULTS

After $<12$ months from the start of the treatment with BPs BRONJ was observed in 10 patients (18%); after 12–24 months in 16 patients (29%); between 24 and 36 months in 10 patients (18%); between 36 and 48 months in 4 patients; and after $>48$ months in 15 patients (Figure 1).

After a median observation time of 28 months (range 4–110 months), no deaths for BRONJ complication were reported. An intact mucosa was observed in 20 patients (37.75%), 21 patients (39.6%) still had an intra-oral lesion with improving secondary infection and pain, the clinical finding was unchanged in 9 patients (16.3%) and 3 patients (5.4%) developed extra-oral fistula and fracture due to extensive osteonecrosis with fracture. Two female patients were not evaluable: one refused any treatment and the other was lost at follow-up. From our data, we found that conservative treatment should be used because it can assure a good quality of life for these patients. Table 4 summarizes the response type obtained with the different proposed treatment.

From the data, it appears that the combination of atb + curettage/sequestrectomy is able to obtain a complete resolution of the BRONJ in $>40$–60% and $>60$% patients, respectively.

A statistical analysis performed considering the percentage of response (resolution, improvement and stabilization/failure) between the two groups of patient treated with or without $O_2$

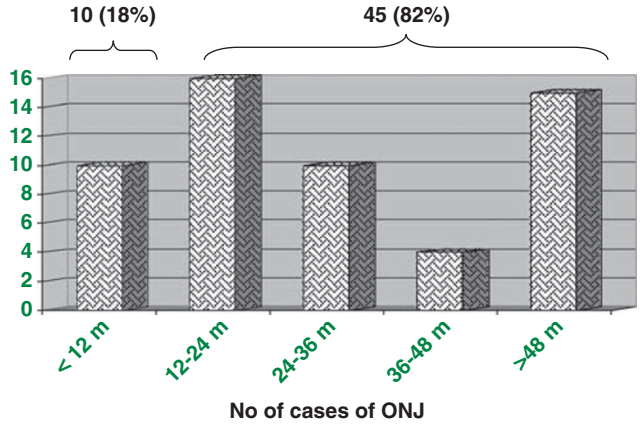


**Figure 1.** The number of cases of BRONJ observed during follow-up (months) after the start of BPs: total number of events 55 cases.

**Table 4.** Response to different treatments in 53 patients[a]

| | *Total patients* | *Resolution* | *Improvement* | *No change/ progression* |
|---|---|---|---|---|
| Antibiotic (Abt) only | 19 | 2 (10.5%) | 10 (52.6%) | 7 (36.9%) |
| Abt+Curettage | 22 | 10 (45.5%) | 9 (40.9%) | 3 (13.6%) |
| Abt+Sequestrectomy | 12 | 8 (66.6%) | 2 (16.7%) | 2 (16.7%) |
| $O_2$ hyperbaric/ ozonotherapy | 27 | 12 (44.4%) | 13 (48.2%) | 2 (7.4%) |
| No $O_2$ hyperbaric/ ozonotherapy | 26 | 8 (30.8%) | 8 (30.8%) | 10 (38.4%) |

[a]Two pts were not evaluable: one refused treatment and one was lost to follow-up.

therapy /ozonotherapy (27 patients, 50.9% vs 26 patients, 49.1%) showed a significant difference ($P<0.007$) in favour of the group treated with $O_2$ therapy/ozonotherapy (Table 5).

Univariate and multivariate analyses were performed to find the different influence of some factors on the evolution of BRONJ: type and total dosage of BPs (80, 100, 110, 120 and 130 mg of zoledronic acid), sex and trigger; none of these factors showed a statistical difference (Table 5). Otherwise, with the *Z*-test for trend, between the number of patients who reached a resolution of BRONJ, we found a statistical difference in the group treated with low dose of zoledronic acid (Figure 2).

## DISCUSSION AND CONCLUSION

BP treatment is generally considered as supportive treatment in neoplastic disease metastasizing to bone. In a large number of trials the efficacy of these drugs, as reduction in pathologic fractures,[19] bone lesions progression has been reported and advantage in progressive free survival and overall survival[26] is reported. The complex mechanisms of action of BPs are under investigation, and not all activities are well known. In our retrospective analysis, we have selected a homogeneous population with MM and WM treated in different haematological departments. Because of their clinical characteristics, MM patients are the best candidates to be treated with BPs. However, because of the prolonged time of BP treatment in MM patients, the BRONJ has been observed more frequently.[32] Despite this, no prospective randomized trials have been designed to clearly define the etiopathology of this complication. The other in our retrospective study, we confirm that the incidence of this complication is between 4 and 15%, and an important factor for BRONJ is the cumulative dosage of BPs received. In the majority of the cases, BRONJ is associated with surgical intervention in the bone of the jaw. In our study, with the longitudinal clinical follow-up of 28 months (range 4–110 months), we demonstrated that the majority of the patients reached the remission of the BRONJ with

**Table 5.** Univariate analysis for the following values

| *Variables* | *Responders* | *Not responders* | P-*value* |
|---|---|---|---|
| *Sex* | | | |
| Males | 29 | 8 | 0.20 |
| Female | 11 | 5 | |
| *$O_2$ therapy* | | | |
| Yes | 25 | 2 | **0.007** |
| Not | 16 | 10 | |
| *Localization* | | | |
| Superior maxilla | 18 | 4 | 0.20 |
| Inferior maxilla | 20 | 7 | |
| *Teeth extration* | | | |
| Yes | 28 | 7 | 0.20 |
| Not | 13 | 5 | |
| *Total dosage of bisphosphonate* | | | |
| $<80$ mg | 19 | 5 | 0.24 |
| $>80$ mg | 22 | 7 | |
| $<100$ mg | 24 | 5 | 0.10 |
| $>100$ mg | 16 | 8 | |
| $<110$ mg | 29 | 6 | 0.14 |
| $>110$ mg | 12 | 6 | |
| $<120$ mg | 34 | 8 | 0.10 |
| $>120$ mg | 7 | 4 | |
| $<130$ mg | 35 | 8 | 0.10 |
| $>130$ mg | 6 | 4 | |
| *Bisphosphonate* | | | |
| Zoledronic acid | 26 | 9 | 0.20 |
| Zoledronic acid plus pamidronate | 14 | 3 | |

As considering the percentage of response (resolution, improvement and stabilization/failure) between the two groups of patient treated with or without $O_2$therapy/ozonotherapy, there is a significance difference ($P<$ 0.007) in the group treated with $O_2$ therapy/ozonotherapy.

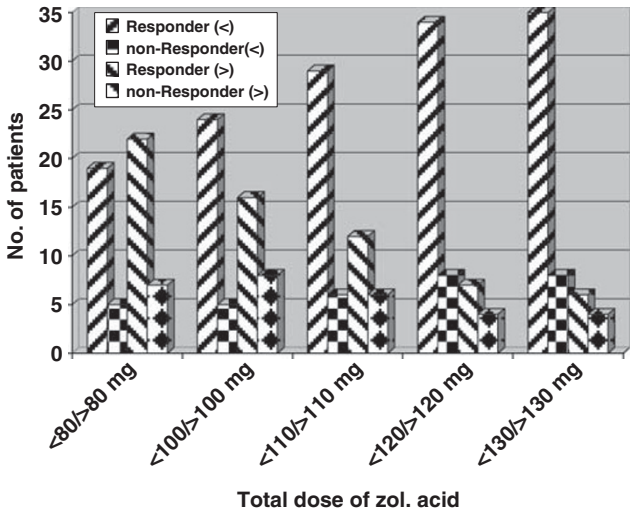


**Figure 2.** Probability of resolution or improvement of BRONJ at different cut-offs of total dosage of zoledronic acid administration ($<80$ vs $>80$ mg; $<100$ vs $>100$ mg; $<110$ vs $>110$ mg; $<120$ vs $>120$ mg; and $<130$ vs $>130$ mg).

conservative treatment and that only in 21.8% of cases surgical treatment and sequestrectomy was necessary (12/53 patients). At the moment, we do not know which is the best treatment for this complication. In our experience, we find that antibiotic treatment is insufficient to reach a resolution but can obtain exclusively a containment of the disease; only 10.5% of patients with BRONJ reached complete response with only antibiotics. If necessary, debridement and sequestrectomy assure most efficacy (45.5% and 66.6% of resolution, respectively). In addition, our data show that $O_2$ hyperbaric/ozonotherapy is very active in the treatment, because 44.4% of patients obtain complete resolution of BRONJ in comparison with 30.8% of patients who did not perform this procedure. In only 7.4% of patients not treated with $O_2$ hyperbaric/ozonotherapy no change or progression of the lesion was seen. These data underline the need for the prevention of the BRONJ.[33]

It is important to evaluate oral situation before and during BP treatment. A dental examination with preventive dentistry must be performed before starting therapy, and some cautions must be used if dental problems appear during therapy. The use of antibiotics for germ eradication, the indication to avoid tooth removal and dental implants and the implementation of non-surgical control of periodontal disease are universally recognized. Treatment and time of BP therapy must be decided in single patients, because only with personalized schedules we can reduce or avoid this complication. The treatment should be used not $>1-2$ years. Antibiotic treatment should be used immediately when the diagnosis is suspected, and conservative surgical approach must been used if necessary. Although BRONJ is a late complication of the use of BPs, this complication interferes with the quality of life of the patients but not on survival, because no death was observed to be due to infective complications during prolonging treatment for MM. The use of new guidelines with the purpose to prevent BRONJ seems to reduce the risk of appearance of this complication.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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