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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INTRODUCTION

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 O2 therapy/ozone therapy and curettage and in 12 with sequestrectomy and O2/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. O2 hyperbaric/ozone therapy 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.

Keywords: bisphosphonate; osteonecrosis; pamidronate; zolendronate; multiple myeloma
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 (49 patients, 79%), 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.16 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 hematological 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 benzidamime (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, O2 hyperbaric/ozone therapy 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 osteotomy. Ozone therapy was performed as described from Petrucci et al.29 Infact, hyperbaric O2 therapy, by locally increasing the O2 content of the blood, produces a significant reduction in the risk of wound infection.31

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 ozone therapy and surgical debridement; 12 patients (22%) required sequestrectomy in association with antibiotic and O2/hyperbaric therapy (Table 3).

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

| Patients | Sex | Median age (range) |
|----------|-----|-------------------|
| 55       | 16 Males; 39 females | 72 years (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  |

**Mean cumulative dose**

| Pamidronate | 1 patient (1.8%) |
| Zoledronic acid | 36 patients (65.5%) |
| Pamidronate/Zoledronic acid | 18 patients (32.7%) |

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

| Site of ONJ | Patients (%) |
|-------------|--------------|
| Mandible    | 29 (52.7%)   |
| Mandible and maxilla | 4 (7.3%) |
| Maxilla     | 22 (40%)     |

| Trigger for ONJ | Patients (%) |
|-----------------|--------------|
| Dentoalveolar surgery (including extractions) | 43 (78.4%) |
| Dental implant placement | 3 (5.4%) |
| Periodontal disease | 5 (9%) |
| Dental prosthesis | 3 (5.4%) |
| No trigger | 1 (1.8%) |

**Table 3. Treatment and response**

| Type of treatment | Patients |
|-------------------|----------|
| Antibiotic only   | 19 patients |
| Antibiotic+curettage | 6 patients |
| Antibiotic+hyperbaric O2/ Ozonotherapy+curettage | 16 patients |
| Antibiotic+hyperbaric O2/ Ozonotherapy+sequestrectomy | 12 patients |
| No treatment      | 2 patients |

**Overall response to treatment**

| Resolution | Improvement | No change | Progression | Not evaluable |
|------------|-------------|-----------|-------------|---------------|
| 20 patients (36.4%) | 21 patients (38.2%) | 9 patients (16%) | 3 patients (0.05%) | 2 patients (3.6%) |

**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 O2.
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, 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

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**Table 4.** Response to different treatments in 53 patients

| Treatment                  | 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%)             |

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

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**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 extraction           |            |                |         |
| 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.
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 exclusive 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 O₂ hyperbaric/ozone therapy 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 O₂ hyperbaric/ozone therapy 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 be 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.

REFERENCES

1 Brown JE, Coleman RE. The role of bisphosphonates in breast cancer: the present and future role of bisphosphonates in the management of patients with breast cancer. Breast Cancer Res 2002; 4: 24 - 29.
2 Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an expert panel. Ann Oncol 2008; 19: 420 - 432.
3 Donath J, Krasznai M, Fornet B, Gergely Jr P, Poor G. Effect of bisphosphonate in an expert panel. J Pharmacol Sci 2004; 53: 1189 - 1199.
4 Bone HG, Hosking D, Devogelaer JD, Tucci JR, Emkey RD, Tonino RP. Ten Years' Experience with Alendronate for Osteoporosis in Postmenopausal Women. N Engl J Med 2004; 350: 1189 - 1199.
5 Zeger N, Keck AV, Fischerstorfer M. Comparative Tolerability of Drug Therapies for Hypercalcaemia of Malignancy. Drug Saf 1999; 5: 389 - 406.
6 Terpos E, Sezer O, Croucher PI, Garcia-Sanz R, Boccadoro M, San Miguel J et al. The antineoplastic role of bisphosphonates: from basic research to clinical evidence. Ann Oncol 2003; 14: 1468 - 1476.
7 Santini D, Vespasiani Gentilucci U, Vincenzi B, Picardi A, Vasuturo F, La Cena A et al. The antineoplastic role of bisphosphonates: from basic research to clinical evidence. Ann Oncol 2003; 14: 2037 - 2039.
8 Mariani S, Muraro M, Panteleoni F, Fiore F, Nuschak B, Peola S et al. Effector gamma delta T cells and tumor cells as immune targets of zoledronic acid in multiple myeloma. Leukemia 2005; 19: 664 - 670.
9 Ruggiero SL, Dodson TB, Assael LA, Landsberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw: 2009 update. J Oral Maxillofac Surg 2009; 67: 6 - 12.
10 Gonzalez- Maes MA, Bagam-Saturn JV. Alendronate-related oral mucosa ulcers. J Oral Pathol Med 2000; 29: 514 - 518.
11 Demerjian N, Bolla G, Spreeux A. Severe oral ulcerations induced by alendronate. Clin Rheumatol 1999; 18: 349 - 350.
12 Marx RE, Stern D ed). Oral and Maxillofacial Pathology: A Rationale for Treatment. Quintessence Publishing: Hanover Park, IL, 2002.
13 Montefusco V, Gay F, Spina F, Miceli R, Maniezzo M, Teresa Ambrosini M et al. Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates. Leuk Lymphoma 2008; 49: 2156 - 2162.
14 Barone A, Kastritis E, Boccadoro M, Gruppo Italiano Studio Linfomi. Leuk Lymphoma 2009; 50: 137 - 145.
15 Petrucci MT, Gallucci C, Agrillo A, Mustazza MC, Foa` R. Role of ozone therapy in the treatment of osteonecrosis of the jaws in multiple myeloma patients. J Oral Maxillofac Surg 2009; 67: 620 - 623.
16 Vellekoop MA, Koka S, Dilla E, Willemsen E, van Dijk-van der Meijden A et al. Bisphosphonate-related osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates: how the knowledge of a phenomenon can change its evolution. Support Care Cancer 2006; 14: 1311 - 1315.
17 Santini D, Vincenzi B, Battistoni F, Vespasiani Gentilucci U, Ruggiero SL, Dodson TB et al. Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw: 2009 update. J Oral Maxillofac Surg 2009; 67: 6 - 12.
18 Mariani S, Muraro M, Panteleoni F, Fiore F, Nuschak B, Peola S et al. Effector gamma delta T cells and tumor cells as immune targets of zoledronic acid in multiple myeloma. Leukemia 2005; 19: 664 - 670.
19 Ruggiero SL, Dodson TB, Assael LA, Landsberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw: 2009 update. J Oral Maxillofac Surg 2009; 67: 6 - 12.
20 Gonzalez- Maes MA, Bagam-Saturn JV. Alendronate-related oral mucosa ulcers. J Oral Pathol Med 2000; 29: 514 - 518.
21 Demerjian N, Bolla G, Spreeux A. Severe oral ulcerations induced by alendronate. Clin Rheumatol 1999; 18: 349 - 350.
22 Marx RE, Stern D ed). Oral and Maxillofacial Pathology: A Rationale for Treatment. Quintessence Publishing: Hanover Park, IL, 2002.
23 Montefusco V, Gay F, Spina F, Miceli R, Maniezzo M, Teresa Ambrosini M et al. Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates. Leuk Lymphoma 2008; 49: 2156 - 2162.
24 Barone A, Kastritis E, Boccadoro M, Gruppo Italiano Studio Linfomi. Leuk Lymphoma 2009; 50: 137 - 145.
25 Petrucci MT, Gallucci C, Agrillo A, Mustazza MC, Foa` R. Role of ozone therapy in the treatment of osteonecrosis of the jaws in multiple myeloma patients. J Oral Maxillofac Surg 2009; 67: 620 - 623.
26 Vellekoop MA, Koka S, Dilla E, Willemsen E, van Dijk-van der Meijden A et al. Bisphosphonate-related osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates: how the knowledge of a phenomenon can change its evolution. Support Care Cancer 2006; 14: 1311 - 1315.
27 Santini D, Vincenzi B, Battistoni F, Vespasiani Gentilucci U, Ruggiero SL, Dodson TB et al. Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw: 2009 update. J Oral Maxillofac Surg 2009; 67: 6 - 12.
28 Mariani S, Muraro M, Panteleoni F, Fiore F, Nuschak B, Peola S et al. Effector gamma delta T cells and tumor cells as immune targets of zoledronic acid in multiple myeloma. Leukemia 2005; 19: 664 - 670.
29 Ruggiero SL, Dodson TB, Assael LA, Landsberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw: 2009 update. J Oral Maxillofac Surg 2009; 67: 6 - 12.
30 Gonzalez- Maes MA, Bagam-Saturn JV. Alendronate-related oral mucosa ulcers. J Oral Pathol Med 2000; 29: 514 - 518.
31 Demerjian N, Bolla G, Spreeux A. Severe oral ulcerations induced by alendronate. Clin Rheumatol 1999; 18: 349 - 350.