Osteonecrosis of the myeloma patients treated with bisphosphonates

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Summary

Osteonecrosis of the jaw (ONJ) has been reported as uncommon but well recognised complication associated with bisphosphonate treatment. Multiple Myeloma (MM) is the pathology most frequently associated with ONJ in the medical and dental papers published over the last years (45% of the ONJ published cases). ONJ appears to be time-dependent with higher risk after long-term use of intravenous (i.v.) nitrogen containing bisphosphonates (eg, pamidronate, zoledronate) in older MM patients. The most frequent site of ONJ is the mandible and previous dental procedures may be a precipitating factor. Most of the ONJ cases presented clinical evidence of bone exposure and pain. There was no significant association between the occurrence of ONJ and the presence of osteolytic lesions, disease status and the use of thalidomide. Different treatments have been proposed, associated or not: medical therapy (eg, antimicrobial oral rinses, antibiotic and antimicotic), surgical therapy (eg, curettage or sequestrectomy) showing low healing rates and uncertain impact on the prognosis and on the outcome.

KEY WORDS: osteonecrosis, multiple myeloma, bisphosphonates.

Introduction

Bisphosphonates, which are powerful inhibitors of bone resorption, are successfully used to treat malignant hypercalcemia and skeletal events associated with multiple myeloma (MM). The clinical practice guidelines by American Society of Clinical Oncology affirmed the role of intravenous (i.v.) bisphosphonates (pamidronate and zoledronate) in the prevention and treatment of MM-related bone disease (1). The introduction of bisphosphonate therapy has improved the quality of life in most MM patients. Over the last years, several reports have described a debilitating complication, so called “osteonecrosis of the jaw” (ONJ), in patients who have received intravenous bisphosphonates in the treatment of their bone disease such as osteoporosis, malignant metastatic bone lesions or MM-related osteolytic lesions (2-5). On the basis of this finding, new guidelines for the use of bisphosphonates in MM were developed by a multidisciplinary panel consisting of hematologists and dental specialists (6).
The exact mechanism that leads to the induction of ONJ is unknown, but a series of risk factors, classified as systemic and local, have been recognized (7). We focus our review on the clinical features and risk factors of ONJ in the subset of patients with MM. We briefly discuss possible underlying mechanisms of etiopathogenesis and summarize current treatment strategies.

Methods

We have reviewed the literature indexed in MEDLINE database from 2003 to December 2006 concerning bisphosphonate-associated ONJ. We have analyzed 213 MM cases reported in some papers selected on the basis of the homogeneity of the issues considered. Information of interest included the type of bisphosphonate (BPP), the duration of the BPP-therapy, the main clinical characteristics of the patient population, the clinical presentation of the ONJ, the risk factors and the main recommendations for preventing, early diagnosing and properly treating this oral complication.

Review

Table I summarizes reported cases of bisphosphonate-associated osteonecrosis of the jaw in 213 MM patients (3-5, 7-22).

Clinical characteristic of the patient population

In the group of MM patients considered, the ratio male-female was 1.7 with the 63.4% of male and 36.6% of female patients. The ONJ was associated with patients in the sixth decade of life. At the moment of diagnosis of ONJ, the mean age was 67 years with a minimum of 44 and a maximum of 87 years.

Type of bisphosphonate drug prescribed

In relation to the type of BPP used, the most common treatment was the combination of pamidronate and zoledronate (40.8%), followed by pamidronate alone (34.4%) and zoledronate alone (24%). The combination of zoledronate and oral bisphosphonates was used in a little percentage of patients (0.8%).

Mean duration of bisphosphonate therapy before of the ONJ onset

The mean time of treatment with BPP before the onset of the ONJ was 34 months (m) (range 6-84) in the patients treated with pamidronate, 15 m (range 9-19) in the patients treated with zoledronate and 42 m (12-60) in those patients under treatment with the combination of pamidronate and zoledronate.

Table I - Jaw osteonecrosis and bisphosphonate treatment in Multiple Myeloma: selected cases reported in the literature indexed from 2003 to December 2006.

Author	N	Gender M/F	Mean age years (range)	BPP type (N)	Mean duration of BPP-therapy months	ONJ site (N)	Dental extraction
Ruggiero et al., '04 (3)	28	16/12	58 (55-87)	Pam (14) Zol (3) Pam+Zol (11)	ns	Mandible (19) Maxilla (8) Mand.+max. (1)	86%^
Lugassy et al., '04 (4)	3	2/1	66 (58-76)	Pam (1) Pam+Zol (2)	Pam 84 Pam+Zol 42; >48	Mandible (3)	33%
Migliorati et al., '05 (5)	3	2/1	62 (56-74)	Pam (1) Pam+Zol (2)	Pam 26 Pam+Zol 30	Mandible (3)	66%
Purcel and Boyd, '05 (8)	3	3/0	76 (73-79)	Pam (2) Zol (1)	Pam 6 Zol ns	Mandible (2) ns (1)	66%
Bagan et al., '05 (9)	9	4/5	62 (45-80)	Pam (2) Zol (3) Pam+Zol (4)	Pam 22 Zol 17 Pam+Zol 46	Mandible (7) Mand.+max.(2)	64%
Carter et al., '05 (10)	2	2/0	60 (57-64)	Pam (2)	Pam 48	Maxilla (1) Mand.+max.(1)	100%
Ficarra et al., '05 (11)	3	1/2	72 (69-76)	Pam (2) Pam+Zol (1)	Pam 27 Pam+Zol 60	Mandible (2) Mand.+max. (1)	67%
Bamias et al., '06 (12)	11	ns*	ns*	Pam (ns*) Zol (ns*) Pam+ Zol (ns*)	28*	Mandible (9) Maxilla (2)	81%
Melo and Obeid, '05 (13)	7	6/1	67 (61-82)	Pam (4) Zol (2) Pam+Zol (1)	Pam 38 Zol 15 Pam+Zol 46	Mandible (5) Maxilla (1) Mand.+max. (1)	71%
Marx et al., '05 (14)	62	ns	ns	Pam (ns*) Zol (ns*) Pam+ Zol (ns*)	Pam 14^ Zol 9^ Pam+Zol 12^	Mandible (ns*) Maxilla (ns*) Mand.+max (ns*)	38%^
Schirmer et al., '05 (15)	4	4/0	69 (55-73)	us		Maxilla Mandible	
Capalbo et al., '06 (16)	9	3/6	65 (44-80)	Pam (2) Zol (4) Pam+Zol (3)	Pam 51 Zol 14 Pam+Zol 37	Mandible (6) Maxilla (3)	100%
Merigo et al., '06 (17)	12	7/5	71 (62-79)	Zol (8) Pam+Zol (4)	Zol 15 Pam+Zol 51	Mandible (8) Maxilla (3) Mand.+max. (1)	58%
Zarychanski et al., '06 (18)	10	6/4	ns	Pam (9)	Pam 37	Mandible (9) Maxilla (1)	30%
Zuazanga et al., '06 (19)	1	1/0	71	Pam+ Zol	Pam+Zol 48	Mandible	100%
Badros et al., '06 (20)	22	17/5	61 (40-78)	Pam (3) Zol (2) Pam+Zol (17)	Pam ns Zol ns Pam+Zol ns	Mandible (15) Maxilla (2) Mand.+max (5)	45%
Tosi et al., '06 (21)	9	ns	ns	Zol	10	Mandible (6) Maxilla (3)	ns
Dimopoulos et al., '06 (22)	15	9/6	64 (26-73)	Pam (1) Zol (7) Pam+Zol (6) Zol+oral BPP (1)	Pam 19^ Zol 19^ Pam+Zol 53^ Zol+oralBPP 21^	Mandible (13) Maxilla (2)	66%

N: number; M: male; F: female; BPP: bisphosphonates; Pam: pamidronate; Zol: zoledronate; ns: not specified; * as regards MM patients; ^: whole series.

Location of ONJ and odontologic antecedents

As to the site of the lesions, in 73.8% of the case they appeared in the mandible, in the 17.9% of the patients in the upper maxilla. In the 8.3% of the patients both jaws were affected.

Clinical form of presentation

The clinical forms of presentation of the bisphosphonate-associated ONJ were various and, in several cases, there are different clinical item combined. Some papers (4, 5, 8, 10, 16-18, 20) provide a detailed description of the clinical presentation of the ONJ in MM patients included in the relative case series. However, the most common symptom was an exposed are of bone, followed by pain, non-healing sockets, secretion of pus from the gingiva, swelling, lower lip dysaestesia or hypoestesia, oroantral fistula, infection and skin fistula (Fig. 1), bone sequestrum, soft tissue lesions, osteomyelitis, pathologic fracture.

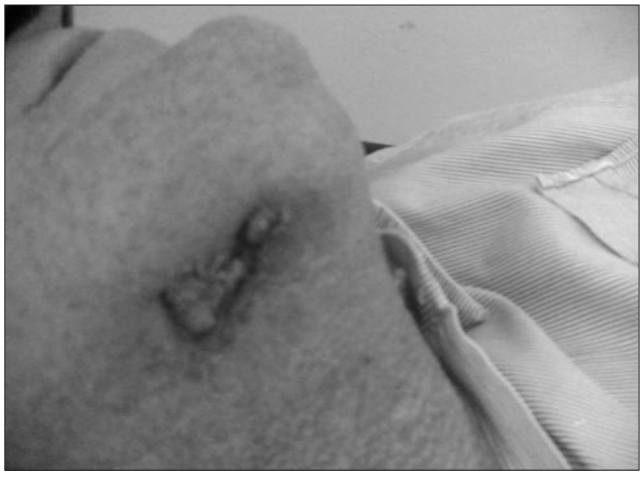

Figure 1 - Infection and skin fistula in a MM patient receiving bisphosphonate treatment.

Other potential risk factors

There was a strong association between bisphosphonate-related ONJ and dental disease or dental procedures including dental surgery. The ONJ appeared after a dental extraction in the 67% of the cases. Chemotherapeutic agents and glucocorticoids, both of which modulate the immunological status of the patients, increase the risk of infection and reduce wound healing, represented potential risk factors for the development of bisphosphonate-associated ONJ in some cases. Nevertheless, neither the impaired bone remodelling related to dexamethasone, nor the antiangiogenic activity of thalidomide seem to be important risk factors for ONJ. In addition, the role of the diabetes in impairing wound healing and promoting bone necrosis was emphasized in some cases (21-23).

Diagnosis of ONJ

The diagnosis of ONJ by means of an orthopantograph raises diagnostic problems particularly in MM patients in whom radiological images of bone lesions, might be erroneously ascribed to the MM (Fig. 2). Computed tomography scan and nuclear magnetic resonance of the jaws, might produce an image of bone necrosis more detailed than that can be achieved by the orthopantograph (Fig. 3).

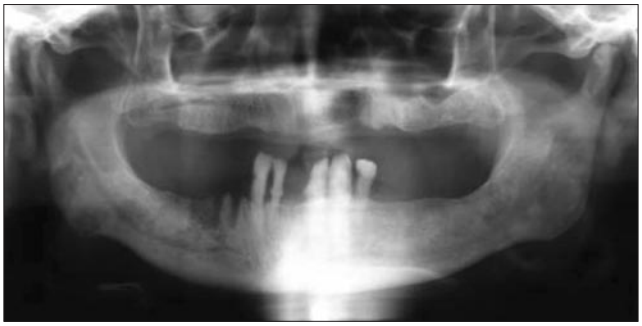

Figure 2 - Radiographic appearance of 1 month post-extractive socket in a MM patient receiving bisphosphonate-treatment, showing no evidence of wound healing.

Treatment of patients with ONJ and prognosis

There is no consensus on management of ONJ in MM patients. Although surgery is potentially curative, postoperative complications were significant and resulted in more bone exposure. Discontinuation of bisphosphonate treatment has not significant helped to either reverse the presence of ONJ or ameliorate symptoms of published cases. In several patients, the ONJ worsened months after stopping bisphosphonate therapy. A different schedule of zoledronic acid perhaps might reduce the risk of the osteonecrosis of the jaw in patients with MM. Hyperbaric oxygen was not helpful in most intervention and it is not

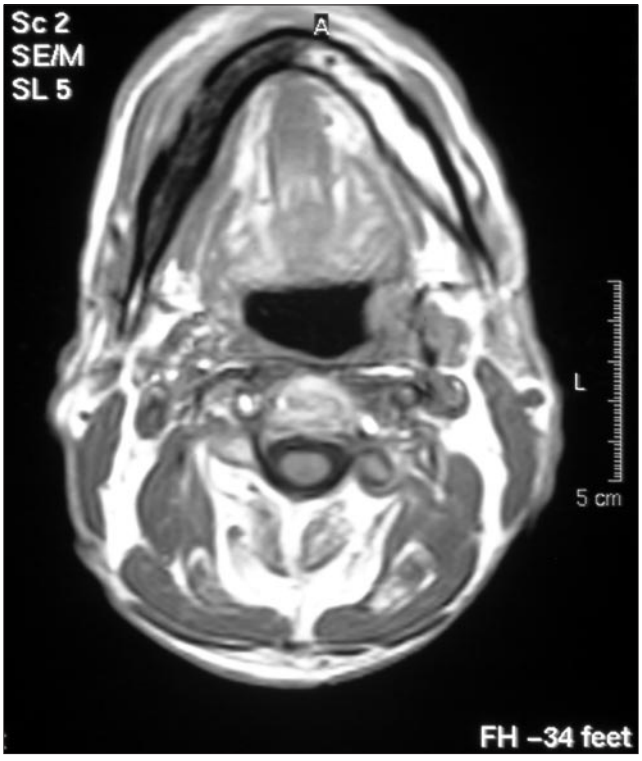

Figure 3: Nuclear magnetic resonance of the previous case shows the effective extension of the disease. Multiple and disomogeneous areas with reduction of the signal involve the right mandibular body.

recommended. For prevention, an aggressive screening and treatment of dental disease should occur before bisphsphonate therapy is initiated (24-26).

Discussion

The MM patients usually receive treatment of skeletal events with intravenous pamidronate and zoledronate which are the most powerful inhibitors of bone resorption within the drug class of bisphosphonates. Multiple Myeloma is the pathology most frequently associated with bisphosphonate-associated ONJ in the medical and dental papers published over the last years.

The pathogenesis of bisphosphonate-associated ONJ remains unclear. Nitrogen-containing bisphosphonates (eg, pamidronate, zoledronate), at the doses found associated with ONJ, are able to inhibit both normal and pathological bone resorption. Alternative pharmacological actions of bisphosphonates, including induction of cell apoptosis, anti-angiogenesis and immune-modulation might also be responsible for the induction of ONJ. Moreover nitrogen-containing bisphosphonates are not metabolized; 50% are secreted unchanged in the urine and the rest bind to bone and is slowly released in into the circulation (27-30).

The true incidence of ONJ in MM is unknown and the percentage of patients suffering this adverse effect associated with bisphosphonate treatment widely varies according to the reports so far published in literature. These differences in incidence may be attributable not only to different methods of survey, but also to specific risk factors working in different patient series considered. The risk for ONJ is substantially higher for patients taking zoledronate and increase over time, probably because of the long-life of these drugs. Another significant factor for ONJ is invasive dental procedures. The increasing risk of ONJ in MM may also be linked to improved patient survival due to the introduction of novel therapeutic such as thalidomide and bortezomib, allowing prolonged exposure to bisphosphonates. However, it remains unclear which patients are at greatest risk for developing ONJ.

Osteonecrosis of the jaw is an important problem in the management of the treatment of the MM patients. It mainly affects MM patients who had received long-term bisphosphonates. ONJ is a debilitating complication, because it interferes with eating, speaking and oral hygiene manoeuvres, and it is, moreover, difficult to treat. Considering the prolonged life expectancy in MM patients and the efforts made to improve their quality of life, it is important to adopt all the precautions, that may reduce the risks of ONJ, early diagnose this complication and treat it properly.

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