Leukemia & Lymphoma, January 2007; 48(1): 56 – 64

informa
healthcare

ORIGINAL ARTICLE: CLINICAL

Bisphosphonate-associated osteonecrosis of the jaw: a review of 35 cases and an evaluation of its frequency in multiple myeloma patients

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(Received 10 July 2006; revised 4 August 2006; accepted 26 August 2006)

Abstract

Over a period of 28 months, we observed five cases of osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates (BP) at our institution. This prompted us to undertake a retrospective, multicenter study to analyse the characteristics of patients who exhibited ONJ and to define the frequency of ONJ in multiple myeloma (MM). We identified 35 cases in Gruppo Italiano Studio Linfomi centers during the period 2002 – 05. The median time from cancer diagnosis to the clinical onset of ONJ was 70 months. In these 35 cases of ONJ, 24 appeared 20 – 60 months after starting BP treatment. The time for the onset of ONJ was significantly shorter for patients treated with zoledronic acid alone than for those treated with pamidronate followed by zoledronic acid. The frequency of ONJ in the MM group during the study period was 1.9%, although the nature of the present study may have resulted in an underestimation of ONJ cases. Our analysis strongly suggested an association between the use of BP and the occurrence of ONJ, although we were unable to identify any definite risk factors with a retrospective study. The most frequently ONJ-associated clinical characteristics were chemotherapy treatment, steroid treatment, advanced age, female sex, anemia, parodonthopaties/dental procedures and thalidomide (in the case of MM patients).

Keywords: *Osteonecrosis, jaw, bisphosphonate, zoledronic acid, multiple myeloma*

Introduction

Osteonecrosis and osteomyelitis are well-recognized conditions, and these disorders can affect any and all of the medullary bones [1], including the jaw. A very early analysis [2] of maxillofacial ischemic osteonecrosis in 1914 referred to a condition of 'chronic osteitis' and, subsequently, different authors have

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ISSN 1042-8194 print/ISSN 1029-2403 online © 2007 Informa UK Ltd.
DOI: 10.1080/10428190600977690

suggested that persistent regional necrosis in osteomyelitis of the jaw was secondary to vascular insufficiency [3–6]. In 1983, a study of the pathophysiology of osteonecrosis induced by radiotherapy in head and neck cancer patients [7] led to a hypothesis suggesting that radiation, tissue hypoxia, hypocellularity and hypovascularity, tissue breakdown, and chronic non-healing wounds could contribute to osteoradionecrosis. A review of 500 cases of medullary and odontogenic disease in painful jaws was published in 2002 [1], and the results showed that 65% of these cases exhibited chronic nonsuppurative osteomyelitis and ischemic osteonecrosis. In approximately 95% of cases, the lesions were directly attributed to impaired blood flow to the jawbone, to the teeth, or to both [1]. An analysis of the risk factors associated with ischemic bone disease revealed several factors, including radiation therapy, chemotherapy, use of steroids, and hormonal therapy. Although previous studies [1,7] had also considered chemotherapy and cancer as possible risk factors for osteonecrosis of the jaw (ONJ), the disorder was in general not frequently described in the years prior to 2003. In those cases in which ONJ was found in cancer patients, it was commonly associated with radiation of the head and neck [1,7]. However, in 2003, a strong emphasis on maxillofacial osteonecrosis emerged when a number of new cases of ONJ were diagnosed in cancer patients treated with bisphosphonates (BP) [8–10].

BP derivatives are potent osteoclast inhibitors that are used extensively in supportive care for cancer patients. No cases of ONJ have been reported in 49 trials for pamidronate and zoledronic acid that enrolled 4829 patients. This could be a factor of time because most trials followed patients for a short period (1–2 years) or missed diagnosis because of a lack of awareness by both patients and physicians. Interestingly, in 2003, Marx [8] described 36 cases and suggested that there was a correlation between treatment with BP and the occurrence of ONJ, and further postulated that the extent of BP-associated ONJ was substantial enough to be termed a 'growing epidemic.' In 2004, Ruggiero et al. [11] published data on 63 cases of ONJ that were diagnosed in the period 2001–03. The author emphasized the growing number of cases in that time period as compared to the years prior to 2001, and noted an association with the use of BP over the same time period. In this context, it is notable that BP-associated ONJ has not been described in the literature prior to 2003.

Interestingly, an analogous condition appeared in the middle of the 19th century in workers who used white phosphorus: Patients displayed an unusual necrosis of the jaw known as 'phossy jaw' or 'phosphorus necrosis' [12]; the phenomenon was related to chronic phosphorus exposure, which produced hyperostosis of the entire skeletal structure [13]. This older observation supports a possible connection between ONJ and the use of the phosphate derivate bisphosphonate: In recent months, hundreds of new cases of ONJ have been described in the literature or presented at hematological and oncological meetings. All of these data strongly support an association between osteonecrosis and BP use [14–31], even though a causal relationship has not been definitively demonstrated.

In our institution, over the course of 28 months, we noted that we identified five cases of ONJ in cancer patients treated with BP. It prompted us to carry out a survey on ONJ cases in our institution as well as at other Gruppo Italiano Studio Linfomi (GISL) centers. The study had two aims: (i) to analyse characteristics of patients and of their associated ONJ independently of their primary diseases [which included multiple myeloma (MM), solid tumors, and other conditions] and (ii) to use a retrospective analysis to try to define the frequency of ONJ in the subgroup of patients who exhibited MM. This study covered a period from 2002–05, which was the same period during which the 35 cases of ONJ were observed in GISL centers. Based on our study results and an analysis of the literature, we suggest a pathophysiological model for BP-associated ONJ.

Materials and methods

Patient study population

We invited each of the 69 GISL centers in Italy to participate in a retrospective multicenter study on ONJ in patients who had received BP treatment. To participate, each center provided data that included details on the characteristics of patients and their cancer, the type and duration of treatment with BP, and the type of cancer treatment, as well as information about odonthoiatric anamnesis, and on the clinical, radiological, microbiological findings of ONJ and biopsy results (if such biopsies were performed). We also evaluated smoking habits, anemia and thrombotic anamnesis. To estimate the frequency of ONJ occurrence in the MM subgroup, we asked each GISL center how many patients affected by MM had been receiving BP treatment in the period 2002–05 (i.e. the same period during which ONJ was reported in this study). Sixteen centers participated in this study reporting 35 ONJ cases.

Diagnostic criteria

There is currently no consensus for the clinical definition of ONJ, and diagnosis is complicated by

the lack of understanding of the pathobiologic mechanisms underlying the disorder. At present, a clinical diagnosis of ONJ is usually made on the basis of visual inspection (e.g. the presence of exposed bone) and/or by the radiographic appearance [32]. The diagnostic criteria utilized in this study included clinical and radiological findings, as well as the exclusion of cancer localization by biopsy (when performed). Exposed bone, fistulas or suspected early manifestations of ONJ (such as tissue swelling or purulent drainage of the mouth) were evaluated by X-ray or a computed tomography (CT) scan. ONJ diagnosis was confirmed by typical radiological findings of osteonecrosis, sequestrum, or lytic lesions with bone sclerosis. In all cases, diagnosis was confirmed by a dentist or maxillofacial surgeon.

Statistical analysis

The statistical analysis of frequencies was performed using SPSS statistical software (SPSS 10.1; SPSS Inc., Chicago, IL, USA). The *t*-test was used to compare the groups treated with the BP derivatives zoledronic acid vs. pamidronate followed by zoledronic acid to compare the time for the onset of ONJ with each treatment.

Results

Sixteen GISL centers participated in this study and 14 centers reported cases of osteonecrosis. ONJ was reported in a total of 35 patients in the period 2002–05, and the number of cases increased every year. Among the reporting institutions, there was one case in 2002, four in 2003, 13 in 2004 and 17 in 2005. The majority of patients presented with pain and oral discomfort; in some cases, there was also numbness of the lips or persistent purulent drainage in the mouth and non-healing wounds. The most relevant clinical findings were red-tissue and soft-tissue swelling and the presence of ulcerated mucosa with yellow–white exposed bone that was surrounded by inflamed soft tissue or by fistulas and abscesses. Table I shows the most relevant patient characteristics, which included type of cancer, type and duration of BP treatment, and number of chemotherapeutic regimens.

In the patient study group, 69% were females and the median age was 70 years. Twenty-eight patients were affected with MM, two with breast cancer, one with prostate cancer, three with steroid-related osteoporosis in myelodisplastic syndrome (MDS), and one with non-Hodgkin's lymphoma; 21 of the total patients had cancerous bone involvement. The median time from diagnosis of cancer to the onset of ONJ was 70 months (Figure 1). All patients were treated with BP derivatives: 14 received zoledronic acid, three received pamidronate, and 18 received pamidronate followed by zoledronic acid. Zoledronic acid was administered at the standard dose of 4 mg every 3–4 weeks; pamidronate was administered at 60–90 mg every 4 weeks. The median duration of treatment with BP was 36 months (range 5–80 months). Twenty-four of the 35 instances of ONJ (68%) occurred 20–60 months after initiation of treatment with BP. The time for the onset of ONJ

Table I. Patient characteristics.

	Number	Median (range)	% of total
Total patients	35		100
Sex			
Male	11		31
Female	24		69
Age (years)		70 (39–80)	
Cancer			
Multiple myeloma	28		83
Solid tumors	3		7
Myelodisplasia	3		7
Lymphoma	1		3
Skeletal involvement			
Yes	22		63
No	13		37
Time from cancer diagnosis (months)		70 (18–89)	
ONJ cases per year			
2002	1		
2003	4		
2004	13		
2005	17		
Cancer treatment			
Chemotherapy	26		74
Steroids	26		74
Thalidomide	13		37
Hormone therapy	2		6
Bone marrow transplant	7		20
Radiotherapy (TBI)	3		8
Prior treatment (*n*)		2 (1–5)	
Type of BP used and time to ONJ development (months)			
All	35	36 (5–80)	
Pamidronate	3	48 (11–68)	
Zoledronic acid	14	20 (5–80)	
Pamidronate followed by Zoledronic acid	18	47 (29–76)	
Time of exposure to BP and number of ONJ cases			
0–20 months	8		23
20–60 months	24		68
>60 months	3		9

development after BP treatment was significantly shorter ($P < 0.001$) for patients treated with zoledronic acid alone (18 months) than for those treated with pamidronate followed by zoledronic acid (48 months) (Figure 2). None of the patients had radiotherapy on the head and neck, although three received total body irradiation before bone marrow transplantation. At the time of diagnosis of ONJ, 27 patients had been treated with chemotherapy; the median for this group was two prior chemotherapy regimens (minimum one, maximum five). The three patients with solid tumors had received both

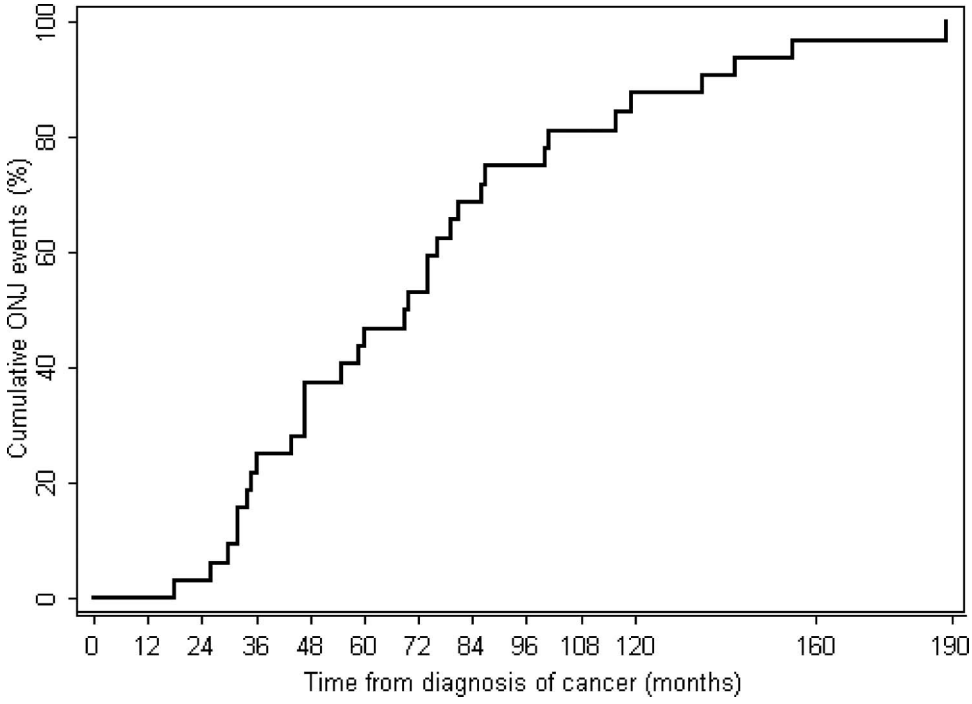

Figure 1. Time from diagnosis of cancer to the onset of ONJ.

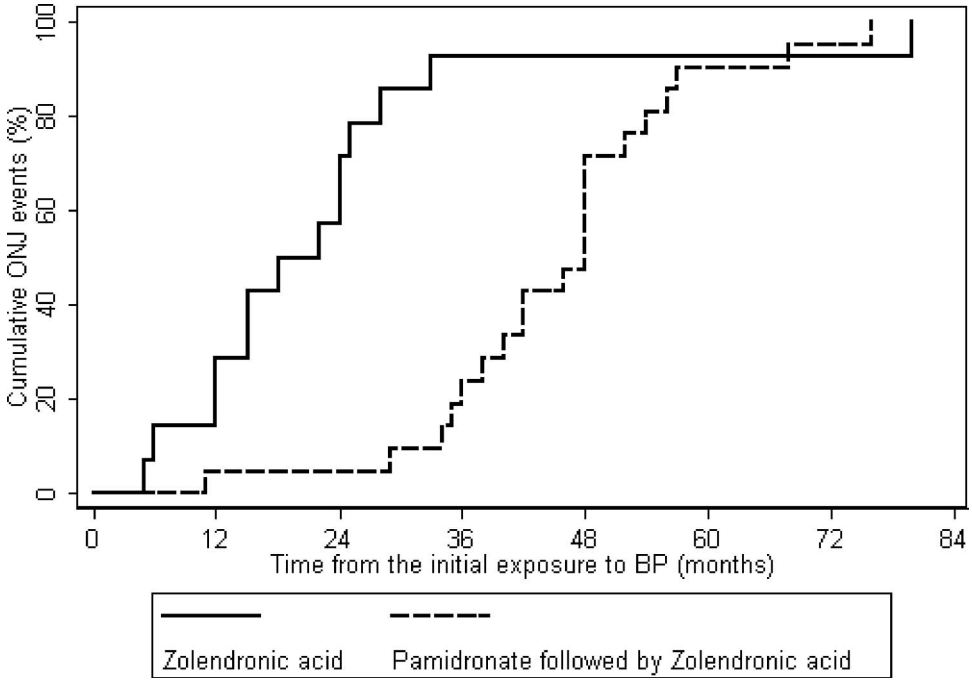

Figure 2. Time from the initial exposure to BP to the onset of ONJ.

chemotherapy and hormonal therapy. All MM patients had received one or more lines of chemotherapy treatment, including vincristine, doxorubicin, and dexamethasone; melphalan and prednisone; cyclophosphamide, steroids, and thalidomide (13 patients) alone or in combination. Some patients also received high doses of melphalan as part of the process of autologous bone marrow transplantation, which was performed in seven cases; one case received an allotransplant. The three MDS patients were treated with steroids.

The most important clinical characteristics of ONJ are reported in Table II. Among the ONJ cases in this study, the mandible was involved in 27 patients, the maxilla in six, and both the maxilla and mandible in two. The right side of the jaw was affected in 14 patients, the left side in 18 patients, and there was bilateral involvement in one case. Almost all cases underwent adiological evaluation with a CT scan, which showed either sequestra of necrotic bone or decreased bone density and lytic lesions with sclerosis. A biopsy was performed in 21 patients: In five cases of MM, the biopsy showed 'lymphoplasmocytic infiltrate', but a light chain evaluation excluded MM localization, although MM localization was unknown for two patients in which the κ and λ chains were not studied. Thus, in 19 out of 21 cases, the localization of neoplasia was excluded. In the majority of cases, the biopsy showed bone necrosis and/or an inflammatory reaction with a leukocyte infiltrate, which is sometimes associated with *Actinomyces*. A microbiological evaluation of the mucosal lesion was performed in 15 cases; 12 patients had a positive evaluation and of those 12, *Actinomyces* was found in eight patients.

In 18 patients, ONJ was apparently spontaneous, in that it also appeared in edentulous areas (eight of these patients used mobile prostheses); in 16 patients, ONJ occurred after dental procedures, but no data on the time between dental procedures and the occurrence of ONJ was available. Parodonthopaties were reported in 17 out of 35 patients. Exposed bone was present in 24 patients, fistulas were present in 14 patients, and abscesses were present in three patients. Several different treatments were used to manage ONJ among the patients in the study group: BP treatment was discontinued in 32 of the 35 patients, local and systemic antibiotics were administered in 33 cases, eight patients underwent hyperbaric oxygen therapy, and 20 patients were treated with surgical debridement. Several patients improved and reported good pain control, but only one patient was reported to be cured.

No risk co-factors could be definitively identified with our retrospective analysis. The most frequent ONJ-associated clinical characteristics were chemotherapy, steroids, advanced age, female sex, anemia, parodonthopaties/dental procedures, and the use of thalidomide (for MM patients). Thrombotic events and smoking habits were rarely found to be associated with ONJ to any notable extent. In the subset of 28 patients with MM (out of the overall group of 35 patients), a total of 13 patients out of 28 (46%) were treated with thalidomide (Table III). The 16 GISL centers that participated in this study

Table II. Characteristics of ONJ.

	Number	% of total
Location		
Maxilla	6	17
Mandible	27	77
Maxilla + mandible	2	6
Right	14	40
Left	18	51
Bilateral involvement	1	3
Unknown	2	6
Onset		
Spontaneous	18*	51
After dental procedures	16	49
Clinical findings		
Pain	30	86
Soft tissue swellling	8	22
Purulent drainage	4	11
Exposed bone	24	69
Fistulas	13	36
Abscesses	3	8
Radiologic findings		
CT scan	25	71
Evidence of osteonecrosis	7	28
Osteolysis and bone sclerosis	13	52
Other radiological definitions	5	20
Biopsy		
Total cases performed	21	60
Negative for neoplasia	19	90
Microbiology		
Total cases with microbiological analysis	15	43
Negative	3	20
Positive	12	80
Actinomyces sp.	8	68
Klebsiella sp.	1	8
Enterococcus sp.	1	8
Pseudomonas sp.	1	8
Candida sp.	1	8
Treatment of ONJ		
BP discontinuation	32	90
Local antibiotics	8	22
Systemic antibiotics	33	92
Hyperbaric oxygen therapy	8	22
Surgical debridement	20	56
Outcome		
No improvement or stable disease	16	46
Improvement	14	40
Cured	1	3
Unknown	4	11

*Eight patients had prostheses.

reported a total of 1402 patients with MM who received BP treatment in the period 2002–05. Of these 1402, only 28 were also diagnosed with ONJ, and the frequency of ONJ occurrence in BP-treated MM patients was 1.9% (Table IV).

Discussion

Osteonecrosis of the jaw is not a new phenomenon in oral medicine, but the frequency of its diagnosis by oncologists and hematologists has notably increased over the last several years. Subsequent to the initial identification of osteoradionecrosis of the jaw in cancer patients treated with radiotherapy on the head and neck some years ago, many new cases of ONJ have emerged in patients treated with BP. Even though it is true that correlation does not necessarily imply causation [33], BP treatment was the common link among 561 cases of ONJ reported by the RADAR group [34], and the evidence linking BP to ONJ has been considered to be level V (using the ASCO scale of evidence rating) [32].

The BP family of compounds is made up of synthetic, nitrogen-containing analogs of inorganic pyrophosphates with a high affinity for calcium, and these analogs are widely used in oncology for their activity as potent inhibitors of osteoclast-mediated bone resorption. Recent results also show that some compounds in the BP family display an antiangiogenic effect in *in vitro* systems and in animal models [35,36]. The potencies of the intravenous BP derivatives pamidronate and zoledronic acid are (respectively) 100- and 10 000-fold greater than that of oral BP etidronate [37], and they are the BP compounds most frequently used as supportive care in cancer patients. It is important to note that our analysis of the possible relationship between BP and ONJ has certain limitations related to its retrospective nature, and is also subject to various biases: the most important of which could be related to a potential increase in physicians' awareness of BP-related adverse events after 2003. In spite of these limitations, the analysis of our data did confirm that all of the 35 cancer patients in this study who developed ONJ had also received nitrogen-containing BP derivatives (pamidronate, zoledronic acid, or both drugs) as part of their treatment regime. The fact that BP treatment was the only common factor among these 35 cancer patients with ONJ strongly suggests that BP usage may play a primary role in creating the pathophysiological conditions that are amenable for ONJ development. This susceptibility is most likely distinct from that of cancer patients who were treated with radiotherapy on the head and neck regions, which has previously been shown to be a risk factor for ONJ development. In our study group, the onset of ONJ occurred 5–80 months after the start of BP treatment and, in 68% of the patients, ONJ onset was apparent 20–60 months after the start of BP treatment.

Although the sample size in this study group is relatively small, we did find statistically significant relationships: the time between the initial BP treatment and the onset of ONJ development in the zoledronic acid group was significantly shorter than the development time in the group that received pamidronate followed by zoledronic acid ($P = 0.001$). This result is in agreement with recent published data [38], and is particularly interesting in light of the fact that zoledronic acid is approximately ten-fold more potent that pamidronate [37]. Based on this data, we hypothesize that BP potency and the duration of BP treatment could be important factors in the development of ONJ. However, because the actual incidence and course of ONJ are poorly documented at this point, it is difficult to draw any firm conclusions in this regard. There are currently only a few reports in the literature on the risk of ONJ development, and estimates from different studies ranged widely: one in 10 000 [39], one in 100 [33], 4–10% [20] or 6.7% [38]. However, these data differ substantially and, to the best of our knowledge, the incidence and prevalence of ONJ has not yet been definitively estimated. It is known that MM is one of the cancers that is most

Table III. Clinical characteristics associated with ONJ development.

	Number	% of total
BP treatment	35	100
Cancer diagnosis	35	100
Chemotherapy treatment	26	74
Steroid treatment	26	74
Age > 65 years	24	69
Female sex	24	69
Anemia	17*	48
Parodonthopaties	17	48
Dental procedures	16	46
Thalidomide treatment	13	46†
Dentures	8	23
Smoking	4	11
Thrombotic events	1	3

*15 patients received erythropoiethin; †percentage calculated only in multiple myeloma patients.

Table IV. Frequency of ONJ in MM patients during 2002–05.

Patients affected by:	
MM and treated with BP (*n*)	1402
ONJ (*n*)	28
Frequency of ONJ (%)	1.9

frequently involved in ONJ development, presumably because BP treatment is used as standard supportive care for the treatment of MM. However, no clear data on the frequency of this phenomenon are available in the literature. The retrospective analysis that we carried out in the resent study included 1402 patients with MM who were treated with BP in the period 2002–05. In this patient group, 28 cases of ONJ were reported, yielding an overall frequency of 1.9%. However, it is possible that because there is no clear consensus on the clinical definition of ONJ, this uncertainty may have affected the accuracy of our retrospective survey of 2002–05 such that ONJ cases may be underestimated.

In our study group, there was an increasing rate of cases from 2002 (one patient) to 2005 (17 cases); this is consistent with other data reported in the literature. It is evident from the literature that ONJ was rarely found in cancer patients in the years prior to 2003 (except for ONJ induced by radiation treatment of the head and neck, as noted above). However, there is no clear explanation for this observation. Our analysis suggests a relationship between BP exposure and ONJ frequency, although it is important to note that the increasing rate of ONJ diagnosis per year could also be related to the increased awareness of these adverse effects. The type of BP derivative used in treatment appears to affect both the likelihood and the timing of the development of ONJ, as demonstrated by our observation that the time between the initiation of BP treatment and the occurrence of ONJ was shorter when patients were treated with zoledronic acid alone vs. pamidronate followed by zoledronic acid.

In this retrospective analysis, all patients who developed ONJ had already been diagnosed with cancer and were receiving BP treatment as part of a supportive care regimen. BP treatment was the only consistent common factor among the ONJ patient group, suggesting that exposure to a BP derivative may be necessary, although perhaps not sufficient, for the development of ONJ (with the exception, as stated above, of those patients who were treated with radiotherapy on the head and neck and thus had another known risk factor for ONJ). However, given the low frequency of ONJ in patients treated with BP derivatives (1.9% in the MM group), it is likely that other associated risk factors also play a role in the development of ONJ. In the present study, the clinical characteristics that were most frequently associated with ONJ included chemotherapy treatment, use of steroids, advanced age, female sex, anemia, parodonthopaties/dental procedures and use of thalidomide (in MM patients). These characteristics could be investigated as possible additional risk factors in future controlled studies. An increased understanding of the factors leading to ONJ development is critical because, although ONJ is a relatively rare complication, it can cause permanent damage and can substantially impair quality of life. Because the currently available therapies are only moderately effective, it is essential to better understand the risk factors for ONJ development so that the condition may be prevented.

Different theories have been advanced to explain how and why ONJ develops [18,19,34] but, because experimental data on the pathogenesis of ONJ are not available, we can only speculate on the real mechanism. On the basis of the results of the present study, and after a thorough analysis of the relevant literature, we propose the following speculative model. We suggest that BP derivatives may act on the bone matrix and on bone vascularization, and that BP action in combination with other risk factors may lead to a complex multistep pathogenesis (Figure 3). Even though BP derivatives act systemically, the disease would tend to be localized specifically to the jaw because of the peculiar anatomy and physiology of that region. The jaw is characterized by age-related degenerative vascular alterations of the alveolar arteries [6,40–43]; these changes are especially pronounced in edentulous areas and are positively correlated with the length of time following extraction of the tooth or teeth. The increased speed of blood flowing through narrowed arteries tends to promote propagation of thrombi [44]. Even if the patients in this study showed negative anamnesis for major thrombosis, they had prothrombotic conditions that included one or more of the following: old age, cancer, chemotherapy, hormonal therapy, steroid use, thalidomide use, or a local inflammatory reaction identified in ONJ biopsy. All of these conditions could act locally as co-factors to promote ONJ development.

Because the jaw receives a large blood supply and also has a fast bone turnover rate that is promoted by the presence of teeth [19], impact loading and odonthoiatric procedures can result in high local concentrations of BP in the jaw. BP accumulation would subsequently produce bone damage by interfering with bone homeostasis in a number of different ways: decreasing bone remodelling by inhibition of osteoclasts, osteoblasts, and osteocytes; increasing bone mineral density, and possibly interfering with the vascular system by inhibiting angiogenesis. Tissue hypoxia at the site of the lesion would be also amplified by anemia or radiotherapy, which would contribute to the development of ONJ along with the other co-factors. Once the bone and vascular system have been damaged, the mucosal trauma induced by mastication, prosthesis, or dental procedures leads to exposure of the necrotic bone. Mucosal breakdown can also facilitate local bone infection by the normal flora of the mouth, which can lead to the

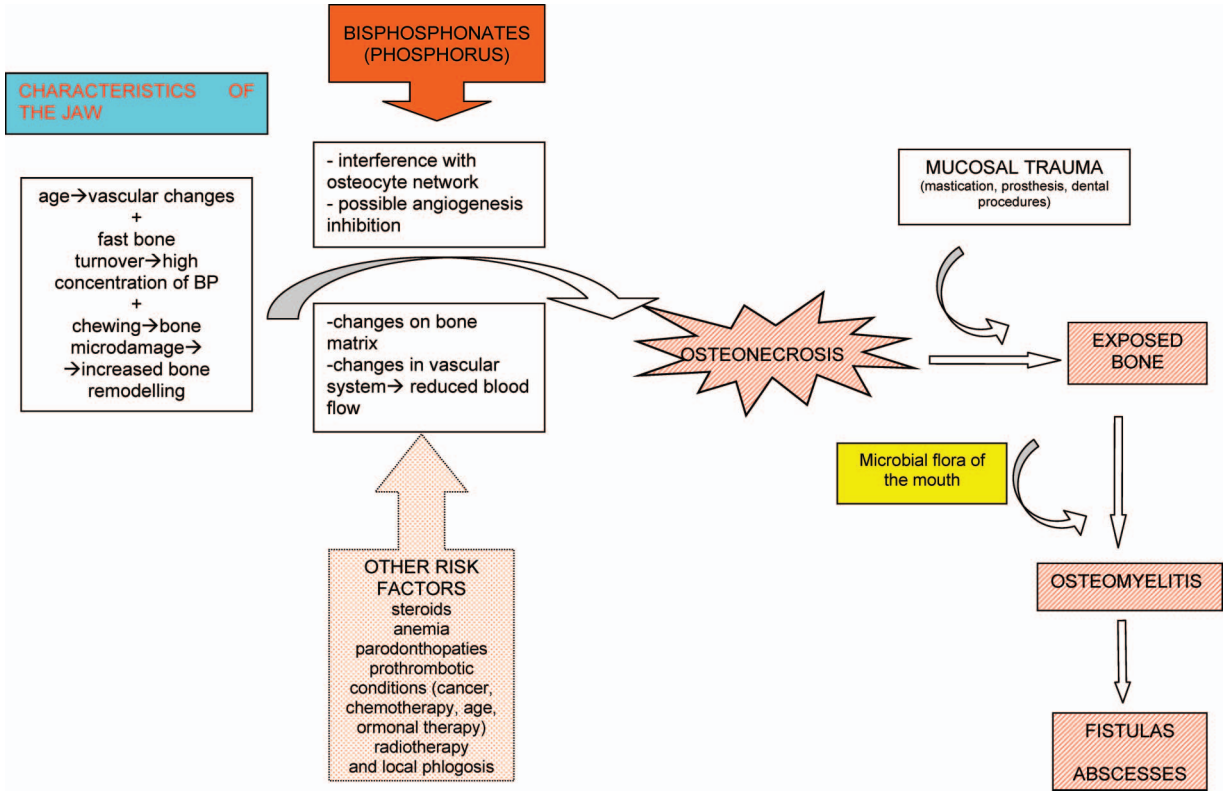

Figure 3. Hypothetical pathobiologic model for the development of BP-associated osteonecrosis. Further details are provided in the text.

development of chronic osteomielytis. Because it is difficult to recover from this condition against the already challenging background of ischemia, the osteomielytis may also promote the formation of abscesses and fistulas.

Taken together, these data suggest that BP-associated ONJ may be viewed as an event that is characterized by multifactor pathogenesis, with BP therapy a necessary pre-condition that subsequently acts in conjunction with other risk factors to facilitate the development of ONJ in a weak region of the skeleton such as the jaw. However, many questions about BP-associated ONJ still remain. One of the most puzzling is why ONJ cases seem to have been identified only recently despite the long history of BP usage as a therapeutic agent. Other areas that need clarification include the general definition of consensus diagnostic criteria, the demonstration of clear risk factors, and the delineation of the pathophysiologic mechanisms underlying ONJ development. Both prospective and biological studies are needed to address these issues.

Acknowledgements

The authors are grateful to the Gruppo Italiano Studio Linfomi (GISL) for their cooperation in this study, and also thank the Associazione Angela Serra per la Ricerca sul Cancro for financial support.

References

1. Shankland WE. Medullary and odontogenic disease in the painful jaw: clinicopathologic review of 500 consecutive lesions. Cranio 2002;20:295–303.
2. Black GV. A Work on Special Dental Pathology, 2nd edn. Chicago, IL: Medico-Dental Co.; 1915. pp. 388–391.
3. Wilensky AO. Osteomyelitis of the jaw. Arch Surg 1932;25:215.
4. Hankey GT. Osteomyelitis (necrosis) of the jaws: its pathology and treatment. Br Dent J 1938;63:552.
5. Brotons A, Penarrocha M. Orofacial neurogenic pain and maxillofacial ischemic osteonecrosis. A review. Med Oral 2003;8157–8165.
6. Bouquot JE, McMahon RE. Neuropathic pain in maxillofacial osteonecrosis. J Oral Maxillofac Surg 2000;58:1003–1020.
7. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. J Oral Maxillofac Surg 1983;41:283–288.
8. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003;61:1115–1118.
9. Wang J, Goodger NM, Pogrel MA. Osteonecrosis of the jaws associated with cancer chemotherapy. J Oral Maxillofac Surg 2003;61:1104–1107.
10. Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. J Clin Oncol 2003;21:4253–4254.

11. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004;62:527–534.
12. Hellstein JW, Marek CL. Bisphosphonate osteochemonecrosis (bis-phossy jaw): is this phossy jaw of the 21st century? J Oral Maxillofac Surg 2005;63:682–689.
13. Heiman H. Chronic phosphorus poisoning. J Indust Hyg 1946;28:142.
14. Pogrel MA. Bisphosphonates and bone necrosis. J Oral Maxillofac Surg 2004;62:391–392.
15. Lugassy G, Shaham R, Nemets A, Ben-Dor D, Nahlieli O. Severe osteomyelitis of the jaw in long-term survivors of multiple myeloma: a new clinical entity. Am J Med 2004; 117:440–441.
16. Assael LA. New foundations in understanding osteonecrosis of the jaws (editorial). J Oral Maxillofac Surg 2004;62:125–126.
17. Greenberg MS. Intravenous bisphosphonates and osteonecrosis (editorial). Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;98:259–260.
18. Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone. An emerging oral complication of supportive cancer therapy. Cancer 2005;104:83–93.
19. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 2005;63:1567–1575.
20. Durie BGM, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005;353:99–100.
21. Woo SB, Hande K, Richardson PG. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005;353:100.
22. Maerevoet M, Martin C, Duck L. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005;353:100–101.
23. Carter G, Goss AN, Doecke C. Bisphosphonates and avascular necrosis of the jaw: a possible association. Med J Aust 2005;182:413–415.
24. Bagan JV, Murillo J, Jimenez Y, Hernandez S, Poveda R, Sanchis JM, et al. Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. J Oral Pathol Med 2005;34:120–123.
25. Vannucchi AM, Ficarra G, Antonioli E, Bosi A. Osteonecrosis of the jaw associated with zoledronate therapy in a patient with multiple myeloma. Br J Haematol 2005;128:738.
26. Ficarra G, Beninati F, Rubino I, Vannucchi A, Longo G, Tonelli P, et al. Osteonecrosis of the jaws in periodontal patients with a history of bisphosphonates treatment. J Clin Periodontol 2005;32:1123–1128.
27. Lenz JH, Steiner-Krammer B, Schmidt W, Feitkau R, Mueller PC, Gundlach KKH. Does avascular necrosis of the jaws in cancer patients only occur following treatment with bisphosphonates? J Craniomaxillofac Surg 2005;33:395–403.
28. Gibbs SDJ, O'Grady J, Seymour JF, Prince HM. Bisphosphonate-induced osteonecrosis of the jaw requires early detection and intervention. Med J Aust 2005;183:549–550.
29. Sanna G, Zampino MG, Pelosi G, Nolè F, Goldhirsch A. Jaw avascular bone necrosis associated with long-term use of bisphosphonates. Ann Oncol 2005;16:1207–1213.
30. Naveau A, Naveau B. Osteonecrosis of the jaw in patients taking bisphosphonates (editorial). Joint Bone Spine 2006;73:7–9.
31. Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol 2006;24:945–952.
32. Schwartz HC. Osteonecrosis and bisphosphonates: correlation versus causation. J Oral Maxillofac Surg 2004;62:763.
33. Bennett CL, Nebeker JR, Lyons EA, Samore MH, Feldman MD, McKoy JM, et al. The Research on Adverse Drug Events and Reports (RADAR) project. JAMA 2005;293:2131–2140.
34. Ruggiero S, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM, et al. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Pract 2006;2:7–14.
35. Wood J, Bonjean K, Ruetz S, Bellahcene A, Devy L, Foidart JM, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther 2002;302:1055–1061.
36. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, Clezardin P. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res 2002;62: 6538–6544.
37. O'Connell MB, Elliot ME. Osteoporosis and osteomalacia In: DiPiro T, editor. Pharmacotherapy: A Pathophysiologic Approach. New York, NY: McGraw-Hill; 2002. p. 1690.
38. Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 2005;23:8580–8587.
39. Chabner BA (editorial). Oncologist 2005;10:301–303.
40. Cohen L. Further studies into the vascular architecture of the mandible. J Dent Res 1960;39:936–946.
41. Oikarinen VJ. The inferior alveolar artery: a study based on gross anatomy and arteriography, supplemented by observations on age changes. Suom Hammaslaak Toim, Finska Tandlakarsallskapets Forhandlingar 1996;61(Suppl 1):1–131.
42. Bradley JC. Age changes of the inferior alveolar artery. Br J Oral Maxillofac Surg 1988;26:517–519.
43. McGregor AD, MacDonald DG. Age changes in the human inferior alveolar artery: a histological study. Br J Oral Maxillofac Surg 1989;27:371–374.
44. Chow TW, Hellums JD, Thiagarajan P. Thrombin receptor activating peptide (SFLLRN) potentiates shear-induced platelet microvesiculation. J Lab Clin Med 2000;135:66–72.