Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid

Meletios A. Dimopoulos
Efstathios Kastritis
Athanasios Anagnostopoulos
Ioannis Melakopoulos
Dimitra Gika
Lia A. Moulopoulos
Christina Bamia
Evangelos Terpos
Konstantinos Tsionos
Aristotelis Bamias

Osteonecrosis of the jaw (ONJ) has been associated with the use of pamidronate and zoledronic acid. ONJ was assessed prospectively since July 2003 in 202 patients with multiple myeloma (MM) who received bisphosphonates since April 1995. Fifteen patients (7.4%) developed ONJ. The median time of exposure to bisphosphonates was 39 months for patients with ONJ compared to 28 months (p=0.048) for patients with no ONJ. The cumulative hazard of developing ONJ was significantly higher in patients treated with zoledronic acid alone than in those treated with pamidronate alone/pamidronate+zoledronic acid/zoledronic acid+ibandronate sequentially (1% at 1 year and 15% at 4 years vs. 0% and 5%, p=0.003). In conclusion, the risk of ONJ is increased with time of exposure and probably with the use of zoledronic acid.

Key words: osteonecrosis, multiple myeloma, bisphosphonates, zoledronic acid.

Haematologica 2006; 91:968-971

From the Dept of Clinical Therapeutics (MAD, EK, AA, DG, AB); Dept of Radiology (LAM), Dept of Hygiene and Epidemiology (CB), Medical School, University of Athens; H. Dunant Hospital, Athens (IM); Department of Hematology, 251 General Air Force Hospital, Athens, Greece (ET, KT).

Correspondence:
Meletios A. Dimopoulos, MD, 227 Kifissias Avenue, Kifissia, Athens 145 61, Greece.
E-mail: mdimop@med.uoa.gr

Bisphosphonates are used for the treatment of bone involvement by multiple myeloma (MM) and solid tumors.[1-3] Recently, avascular osteonecrosis of the jaw (ONJ) has been associated with their use.[3-10] Osteonecrosis refers to the death of bone as a result of impaired blood supply. ONJ has been described in association with the use of zoledronic acid and pamidronate in various malignancies and it has been suggested that its development requires a long period of exposure.[4,5] The diagnosis of osteonecrosis, in most cases, has been made retrospectively, based on a review of medical records rather than by a specialist. Furthermore, a denominator for the patients who were diagnosed with OJN was not established.

In order to define the incidence of ONJ as well possible risk factors we have been prospectively studying the development of ONJ since 2003, while all patients who received bisphosphonates in our department over an 8-year period have been entered into a database. A first analysis, including all patients with malignant bone disease, has already been reported.[11] Nevertheless, such an analysis may not be representative of the problem in each malignancy, since there are differences associated with the duration of treatment. Additionally, biological differences associated with the development of ONJ in different tumors cannot be excluded. That initial report included 111 patients with MM. In our current report, another 91 patients have been added. We, therefore, studied the incidence and possible risk factors associated with bisphosphonate treatment separately in patients with MM.

Design and Methods

Since July 2003 possible osteonecrosis was evaluated prospectively, while all MM patients treated with bisphosphonates (prior to and after that date) have been entered into a database, which includes accurate information on the type and duration of exposure to bisphosphonates. ONJ was diagnosed by a maxillo facial surgeon (IM) based on the following criteria: exposed bone in the maxilla or mandible, associated or not with pain and soft-tissue swelling; unhealed necrotic bone (more than one month) usually (but not necessarily) after dental work; poorly demarcated radio-opaque area of the affected bone on X-ray. Biopsy was performed if exclusion of myelomatous involvement was necessary. The medical records of all patients were reviewed in order to exclude symptoms and signs of ONJ: no patient with a high probability of ONJ was identified. In this analysis we included patients who started treatment with a bisphosphonate up to June 2005 and received at least six infusions. Patients were followed up until November 2005. Pamidronate, zoledronic acid and ibandronate were administered as already reported.[11] Regarding chlodronate and residronate, one month of treatment was considered as one cycle. Bisphosphonate treatment was stopped in patients who developed osteonecrosis.

Statistical analysis

All analyses were performed using the SPSS statistical software (SPSS for Windows, version 12.1, SPSS Inc Chicago, IL, USA). χ^2 tests were used for comparisons of categorical variables. Survival analysis was used to estimate the hazard of developing osteonecrosis, with time of exposure to bisphosphonates being the primary time variable. Hazard functions of developing ONJ according to the use of thalidomide (yes, no) and type of bisphosphonates used (zoledronic acid vs. pamidronate/ibandronate + zoledronic acid) were compared using the log rank test. Throughout the analysis a level of 5% was used to denote statistical significance.

Results and Discussion

Exposure to bisphosphonates and development of osteonecrosis

The earliest bisphosphonate treatment was in April 1995. The characteristics of the 202 patients included in our analysis are shown in Table 1. Most patients received pulsed dexamethasone 40 mg for 4 days every 4 weeks as part of their initial or salvage treatment. Time of exposure to bisphosphonates was significantly associated with the development of ONJ (Table 2). The median time of exposure to bisphosphonates was 39 months for patients with osteonecrosis (11-76), compared to 28 (4.5-123) for patients with no osteonecrosis (p=0.048). In addition, ONJ occurred significantly earlier among patients receiving only zoledronic acid than among patients receiving the other regimes (30 months vs. 62 months, p=0.009).

Table 2 shows the cumulative hazard at various time points after the initiation of treatment with bisphosphonates. The cumulative hazard rose above 1% after 12 months of treatment up to 13% at 4 years. A significant difference in the respective hazards of developing ONJ was found between patients treated with zoledronic acid alone and those treated with pamidronate+zoledronic acid or zoledronic acid+ibandronate (p=0.003) (Figure 1A). The hazard was 1% within the first year of treatment rising to 15% at 4 years for patients treated with zoledronic acid, while the hazard among the other group was 0% for the first year rising to only 5% after 4 years of treatment (Table 2). We also compared the hazards of developing ONJ between different levels of the indicated factors, at 60 months after treatment initiation. This time point was chosen since it was the maximum time of exposure of the subgroup with the smallest range of exposure, i.e. the zoledronic acid group. All patients who received treatment beyond this point were censored. Again the hazard was significantly higher in the zoledronic acid group compared to in the groups receiving pamidronate+zoledronic acid or zoledronic acid+ibandronate (p=0.001) (Figure 1B).

Characteristics and management of patients with ONJ

Nine men and six women developed ONJ. No patient had received radiation to the area of the head and neck. The mandible was involved in 13 patients and the maxilla in two cases. Ten patients had had dental extractions within the year preceding the diagnosis of osteonecrosis, while another three patients had artificial dentures. Biopsy was performed in five cases: necrotic bone was the only histological finding, with surrounding bacteria but no evidence of bacterial invasion in the area of necrosis. Initial management in all cases was conservative. Only minor debridement procedures were attempted. All patients received multiple courses of antibiotics and improvement of oral hygiene was recommended. Measures were taken in order to reduce the contact of artificial dentures with the exposed bone. Treatment with antibiotics resulted in transient improvement, but only one patient showed sustained improvement of osteonecrosis after multiple courses of antibiotics. The other 14 patients, after a minimum follow-up after the development of osteonecrosis of 9 months (range 9-30 months) have persistent disability, mainly consisting of recurrences of purulent discharge and pain. In four cases osteonecrosis was complicated by abscess formation, which led to a fistula in two cases. One patient received hyperbaric oxygen without improvement.

Bisphosphonate-associated ONJ is a well established entity but most studies have not attempted to determine the actual risk of developing this complication. Recently, the International Myeloma Foundation reported that ONJ occurred in 6.8% of 1203 patients with MM and breast cancer receiving bisphosphonates.[12] Although this web-based survey offered valuable information, it suffers from certain limitations. Retrospective studies are subject to

Table 1. Patients' characteristics.

	Osteonecrosis		
	Yes	*No*	*p value*
Sex			
Male	9 (8.7%)	94 (91.3%)	0.468
Female	6 (6%)	93 (94%)	
Age, years			
Median	64	65	0.330
Range	26-73	24-86	
Type of bisphosphonate			
Zoledronic acid	7 (7.5%)	86 (92.5%)	0.838
Pamidronate	1 (3%)	32 (97%)	
Ibandronic acid	0 (0%)	2 (100%)	
Pamidronate+Zoledronic acid	6 (9.1%)	60 (90.9%)	
Zoledronic acid+Ibandronic acid	1 (25%)	3 (75%)	
Pamidronate+ Ibandronic acid	0(0%)	2(100%)	
Chlondronate+Zoledronic acid	0(0%)	1(100%)	
Residronate+Zoledronic acid	0(0%)	1(100%)	
Thalidomide use			0.977
Yes	8 (7.5%)	99 (92.5%)	
No	7 (7.4%)	88 (92.6%)	
Cycles of bisphosphonate treatment	*Median*	*Range*	
All patients	24	6-106	
Zoledronic acid	17	6-60	
Pamidronate	15	6-70	
Ibandronic acid	13.5	7-20	
Pamidronate+Zoledronic acid	45.5	9-106	
Zoledronic acid+Ibandronic acid	20.5	15-45	
Pamidronate+ Ibandronic acid	16	12-20	
Chlondronate+Zoledronic acid	50	N/A	
Residronate+Zoledronic acid	33	N/A	
Time of exposure (months)	*Median*	*Range*	
All patients	29	4.5-123	
Zoledronic acid	19	4.9-85	
Pamidronate	19	4.5-105	
Ibandronic acid	13	5-21	
Pamidronate+Zoledronic acid	53.4	9.4-123	
Zoledronic acid+Ibandronic acid	21.5	16-51	
Pamidronate+ Ibandronic acid	18.3	12-24	
Chlondronate+Zoledronic acid	50	N/A	
Residronate+Zoledronic acid	35	N/A	

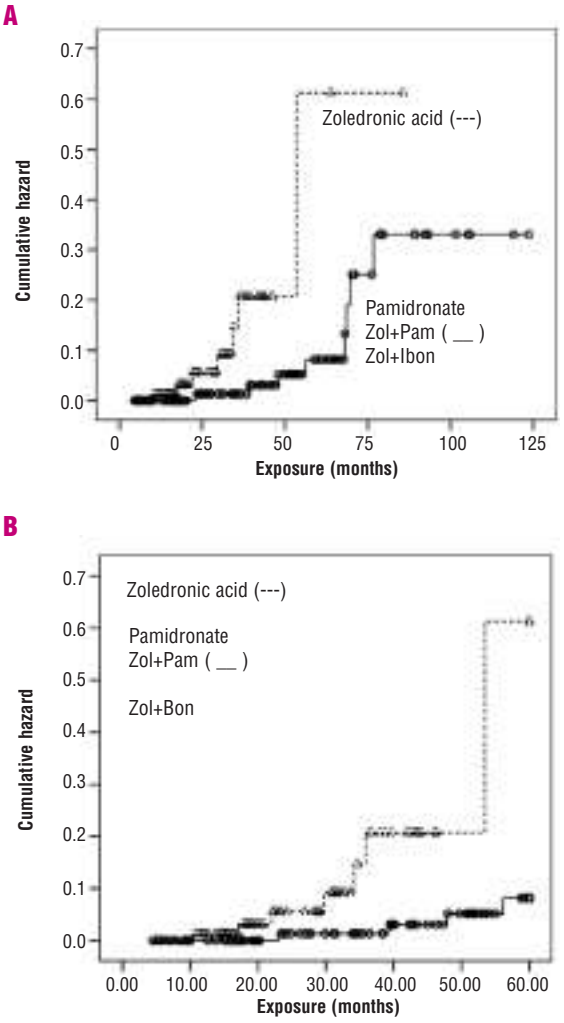

Figure 1. Cumulative hazard of developing of osteonecrosis of the jaw according to treatment with zoledronic acid or pamidronate + zoledronic acid/ibandronate + zoledronic acid according to time of exposure (A) and when patients receiving treatment for more than 60 months were censored irrespective of later development of osteonecrosis (B).

Table 2. Incidence of osteonecrosis according to exposure and type of bisphosphonate.

	Osteonecrosis		
	Yes	*No*	*p*
Median no. of cycles			
All patients	30 (n=15)	23 (n=187)	0.207
Zoledronic acid	25 (12-42) (n=7)	17 (6-60) (n=86)	0.243
Pamidronate	49 (n=1)	15 (n=32)	
Pamidronate+Zoledronic acid	50 (n=6)	45 (n=60)	0.547
Zoledronic acid+Ibandronic acid	23 (n=1)	20 (n=3)	
Zoledronic acid	25 (12-42) (n=7)		0.072
Pam, Pam+Zol, Zol+Ib	45 (9-69) (n=8)		
Median exposure (months)			
All patients	39 (n=15)	28 (n=187)	0.048
Zoledronic acid	30 (11-53) (n=7)	19 (5-85) (n=86)	0.185
Pamidronate	68 (n=1)	19 (n=32)	
Pamidronate+Zoledronic acid	62 (n=6)	53 (n=60)	0.532
Zoledronic acid+Ibandronic acid	23 (n=1)	21 (n=3)	
Zoledronic acid	30 (11-53) (n=7)		0.009
Pam, Pam+Zol, Zol+Ib	62 (23-76) (n=8)		

	Cumulative hazard (% [95%CI])			
	12 mo	24 mo	36 mo	48 mo
All patients (n=202)	1[0-2]	3[1-4]	6[2-10]	13[5-21]
Zoledronic acid (n=93)	1[0-3]	5[0-11]	15[3-27]	15[3-27]
Pam, Pam+Zol, Zol+Ib (n=103)	0[0]	1[0-3]	1[0-3]	5[0-11]

biases due to the increased awareness of this side effect since 2003. Patients with dental problems may also have been more responsive to a web-based survey. We reported the first attempt to study the development of osteonecrosis prospectively,[11] which, we believe, overcame some of the limitations of the previous reports and provided a denominator for the development of ONJ. The current series, although including the 111 MM patients of the first study, we believe, offers important information for the following reasons: we only analyzed patients with MM, who may be at higher risk of developing ONJ than other cancer patients;[12] we included another 91 patients, thus almost doubling the number of MM patients analyzed in the first report; the study period has been extended and this makes our results more accurate, given the association of ONJ with the time of exposure. Furthermore, we now provide longer follow-up data regarding the outcome of ONJ in the patients who developed this complication. A limitation of our study is that information regarding previous bisphosphonate use is retrospective. Thus we cannot exclude that a few cases of ONJ may have been missed. Nevertheless, this is unlikely, since ONJ causes intense symptoms, which cannot remain unrecognized, and our retrospective review of the medical records of the patients did not reveal any case with probable ONJ.

The incidence of osteonecrosis was 7.4%, similar to that reported by Durie *et al.* (6.8%).[12] Consistent with our first report,[11] as well as with other observations,[13,14] we found that time of exposure to the drug is a significant risk factor for the development of ONJ. The type of bisphosphonate also seems to represent a significant risk factor in the development of ONJ. We observed only one case of ONJ in patients treated with pamidronate alone, while all other cases were associated with the use of zoledronic acid either alone or in combination with pamidronate or ibandronate. The median time of exposure to bisphopshonates was more than halved when zoledronic acid was used alone. The fact that zoledronic acid has been available for a much shorter period of time than pamidronate may have introduced some bias in this analysis. Ideally the two compounds should be directly compared prospectively. In order to address this issue more accurately, we examined the incidence of ONJ by censoring all patients who did not develop the complication at 5 years. Although this analysis is not a substitute for a prospective comparison, we believe that it is the only meaningful way

of extracting information about possible differences between the two bisphosphonates. These results, combined with supportive data from other studies,[12,13] indicate that zoledronic acid is associated with a higher risk of developing ONJ. The reason for this difference is unknown. A possible explanation is the more potent inhibitory effect of zoledronic acid on bone turnover and a stronger anti-resorptive activity compared with pamidronate.[16,17] Based on the above data, we suggest that the incidence of ONJ should be reported in association with the time of exposure and the type of the agent used, in order to be able to compare data between different series. The estimated incidences of ONJ after 3 years of exposure are fairly similar in our study (15%) and the web-based survey of the International Myeloma Foundation (10%) with zoledronic acid alone.[12]

Our analysis suggests a sustained increase in the risk of developing ONJ after 4 years of exposure. Taking into consideration the natural history of MM, bisphosphonates may be administered to some patients for several years. The longest duration of bisphosphonate treatment in large studies has been 2 years.[4,18,19]

In view of the data reported by us as well as by others, caution should be exercised when using pamidronate and zoledronic acid for more than 2 years. Our data and those of other studies indicate that dental extraction, artificial dentures and periodontitis predispose to the development of ONJ. Avoidance of invasive dental procedures and improved oral hygiene may, therefore, reduce the incidence of this complication. Oncologists and dentists should be aware of this complication and its management. Risk factors, such as the time of exposure to bisphosphonates, the type of bisphosphonate and dental procedures, should be identified. These points are emphasized by new post-marketing guidelines issued for pamidronate and zoledronic acid.[20]

Although we discontinued bisphosphonates after the development of osteonecrosis, no improvement was observed. This underlines the importance of prevention of this complication and suggests that the decision concerning further treatment should be mainly based on the derived or expected benefit. Discontinuing bisphosphonates leads to a marked increase in bone resorption, which can lead to an increased risk of bony complications. In conclusion, ONJ is a complication of bisphosphonate treatment, associated with the time of exposure to this treatment in patients with MM. The risk appears to be higher with zoledronic acid than with pamidronate. The identification of additional risk factors and improvement in the management of this complication will result in safer long-term use of bisphosphonates in MM.

MAD: contribution of most patients with multiple myeloma, conception, acquisition, analysis and interpretation of data, final approval; EK, AA: acquisition, analysis and interpretation of data, final approval; IM: diagnosis and management of all patients with osteonecrosis, final approval; DG, LAM, CB: acquisition, analysis and interpretation of data, final approval; ET: contribution of patients with multiple myeloma, critical revision of the manuscript, final approval; KT: contribution of patients with multiple myeloma, interpretation of data, final approval; AB: acquisition, analysis and interpretation of data, drafting of the manuscript, final approval. The authors declare that they have no potential conflicts of interest.

Manuscript received January 11, 2006. Accepted May 8, 2006.

References

1. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med 2005;352:373-9.
2. Berenson JR, Hillner BE, Kyle RA, Anderson K, Lipton A, Yee GC, et al. American Society of Clinical Oncology Clinical Practice guidelines: the role of bisphosphonates in multiple myeloma. J Clin Oncol 2002;20:3719-36.
3. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. N Engl J Med 1996;334:488-93.
4. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003;61: 1115-7.
5. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroft SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004;62:527-34.
6. Durie BGM, Katz M, McCoy J, Crowley J. Osteonecrosis of the jaws in myeloma: time dependent correlation with Aredia and Zometa use. Blood 2004;104 Suppl 1:216a[abstract].
7. Bagan JV, Murillo J, Jimenez Y, Poveda R, Milian MA, Sanchos JM, et al. Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. J Oral Pathol Med 2005; 34:120-3.
8. Melo MD, Obeid G. Osteonecrosis of the maxilla in a patient with a history of bisphosphonate therapy. J Can Dent Assoc 2005;71:111-3.
9. Vannucchi AM, Ficarra G, Antonioli E, Bosi A. Osteonecrosis of the jaw associated with zoledronate therapy in a patient with multiple myeloma [letter]. Br J Haematol 2005;128:738.
10. Migliorati CA. Bisphosphanates and oral cavity avascular bone necrosis [letter]. J Clin Oncol 2003;21:4253-4.
11. 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;23:8580-7.
12. Durie GM, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005;353:99-100.
13. Durie BGM, Katz M, McCoy J, Crowley J. Osteonecrosis of the jaws in myeloma: analysis of risk factors including time dependency of Aredia and Zometa use, steroid use and underlying dental problems. Haematologica 2005; 90:190[abstract].
14. Singhal S, Kut V, Tariman J. Pamidronate and zoledronate-associated osteonecrosis in myeloma is an increasing and under-recognized problem. Haematologica 2005;90:191[abstract].
15. Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. Bone 1996;18:75-85.
16. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 2001;7:377-87.
17. Hortobayi GN, Theriault RL, Lipton A, Porter L, Blayney D, Sinoft C, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. J Clin Oncol 1998; 16:2038-44.
18. Lipton A, Theriault RL, Hortobayi GN, Simeone J, Knight RD, Mellans K, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases. Long-term follow up of two randomized, placebo-controlled trials. Cancer 2000; 88:1082-90.
19. Package Insert Revisions re: Osteonecrosis of the jaw. Zometa (zoledronic acid) injection and Aredia (pamidronate disodium) injection. Oncologic Drugs Advisory Committee Meeting. March 4, 2005. Accessed at http://www.fda.gov.