VOLUME 23 · NUMBER 34 · DECEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Osteonecrosis of the Jaw in Cancer After Treatment With Bisphosphonates: Incidence and Risk Factors

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Submitted May 27, 2005; accepted August 18, 2005.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2334-8580/$20.00

DOI: 10.1200/JCO.2005.02.8670

ABSTRACT

Purpose
Osteonecrosis of the jaw (ONJ) has been associated recently with the use of pamidronate and zoledronic acid. We studied the incidence, characteristics, and risk factors for the development of ONJ among patients treated with bisphosphonates for bone metastases.

Patients and Methods
ONJ was assessed prospectively since July 2003. The first bisphosphonate treatment among patients with ONJ was administered in 1997. Two hundred fifty-two patients who received bisphosphonates since January 1997 were included in this analysis.

Results
Seventeen patients (6.7%) developed ONJ: 11 of 111 (9.9%) with multiple myeloma, two of 70 (2.9%) with breast cancer, three of 46 (6.5%) with prostate cancer, and one of 25 (4%) with other neoplasms ($P = .289$). The median number of treatment cycles and time of exposure to bisphosphonates were 35 infusions and 39.3 months for patients with ONJ compared with 15 infusions ($P < .001$) and 19 months ($P = .001$), respectively, for patients with no ONJ. The incidence of ONJ increased with time to exposure from 1.5% among patients treated for 4 to 12 months to 7.7% for treatment of 37 to 48 months. The cumulative hazard was significantly higher with zoledronic acid compared with pamidronate alone or pamidronate and zoledronic acid sequentially ($P < .001$). All but two patients with ONJ had a history of dental procedures within the last year or use of dentures.

Conclusion
The use of bisphosphonates seems to be associated with the development of ONJ. Length of exposure seems to be the most important risk factor for this complication. The type of bisphosphonate may play a role and previous dental procedures may be a precipitating factor.

J Clin Oncol 23:8580-8587. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Bisphosphonates are synthetic analogs of the naturally occurring pyrophosphate. They accumulate to sites of active bone formation, making the sites more resistant to dissolution by osteoclasts, and are internalized by osteoclasts reducing their survival and modulating the signaling from osteoblasts to osteoclasts.[1] During the last decade, more potent bisphosphonates have been used.[2]

Bisphosphonates have been approved for the treatment of cancer-related hypercalcemia and bone involvement by multiple myeloma (MM) and solid tumors.[3-7] Adverse effects associated with the use of bisphosphonates are infrequent and consist of pyrexia, renal function impairment, and hypocalcemia. Recently, a new complication associated with their use has been described: avascular osteonecrosis of the jaw (ONJ).[8-15] ONJ was initially associated with the use of zoledronic acid but occurrences after pamidronate use have also been

reported.[8,9] Several issues need to be clarified: the pathophysiologic mechanism underlying ONJ, and the incidence, possible risk factors, prevention, and appropriate treatment. Bisphosphonate-associated ONJ has been described in various malignancies and it has been suggested that its development requires a long period of exposure.[9,10] The diagnosis of osteonecrosis, in most cases, was made retrospectively, based on the review of medical records rather than by a specialist. Furthermore, a denominator for the patients who were diagnosed with ONJ was not established.

After the first reports of ONJ appeared in the literature, every patient in our center who was treated with bisphosphonates and had dental problems was assessed by a maxillofacial surgeon who confirmed the diagnosis and treated the patient. To define the incidence of ONJ as well as its association with specific risk factors, we analyzed the medical records of all patients with cancer who received bisphosphonates in our department during an 8-year period.

PATIENTS AND METHODS

Our first patient with bisphosphonate-associated ONJ was diagnosed in July 2003. Since then, 16 additional patients receiving bisphosphonates were prospectively diagnosed with ONJ. The diagnosis of ONJ was suspected by the presence of symptoms and signs, such as pain, soft-tissue swelling, or exposed bone, especially after dental work. All patients with suspected ONJ were referred to a maxillofacial surgeon (I.M.) for additional evaluation and treatment. All patients had panoramic x-rays to rule out other etiologies, whereas biopsy was performed only when exclusion of metastatic disease was necessary. The earliest initiation of bisphosphonate treatment among these patients was in 1997. Therefore, we studied patients who were treated with bisphosphonate from January 1, 1997. The medical records of all patients who were included in the analysis were reviewed to exclude symptoms and signs of ONJ: no patient with a high probability of ONJ was identified.

To ensure adequate exposure to the drugs, we included patients who started treatment with a bisphosphonate until December 31, 2003 and received at least six infusions. Patients were observed until February 2005. Pamidronate at 90 mg was administered as a 2-hour infusion every 4 to 5 weeks, zoledronic acid was administered at 4 mg every 4 to 6 weeks during 15 minutes, and ibandronate was administered at 4 mg during 2 hours every 4 to 6 weeks. Patients who developed osteonecrosis were no longer treated with bisphosphonates.

Statistical Analysis

Time of exposure to bisphosphonates was defined as the time in months from the initial infusion of bisphosphonates to the last recorded infusion. All analyses were performed using the SPSS statistical software (SPSS for Windows, version 12.1; SPSS Inc, Chicago, IL). The χ^2 test was used for comparisons of proportions across levels of categoric variables. For continuous variables, the *t* test or the Mann-Whitney *U* test was used for the comparison of the means or the medians, respectively. Survival analysis was used to estimate the hazard of developing osteonecrosis; time of exposure to bisphosphonates was the primary time variable. In this analysis, subjects who did not develop osteonecrosis while receiving treatment were censored, whereas the focal event was diagnosis of osteonecrosis. Hazard functions of developing ONJ according to the use of thalidomide (yes or no), primary site (myeloma, breast, or prostate), and type of bisphosphonate used (zoledronic acid *v* pamidronate ± zoledronic acid) were compared using the log-rank test. Throughout the analysis, a level of 5% was used to denote statistical significance.

RESULTS

Patients

The baseline characteristics of the 252 patients included in our analysis are listed in Table 1. Other diagnoses included carcinoma of the lung (n = 7), cervix (n = 3), bladder (n = 4), endometrium (n = 3), unknown origin (n = 2), stomach (n = 1), kidney (n = 1), ovaries (n = 1), colon (n = 1), lymphoma (n = 1), and Langerhans cell histiocytosis (n = 1). One hundred five patients were treated with zoledronic acid, 58 patients were treated with pamidronate, and five patients were treated with ibandronate, whereas 69 patients received pamidronate and zoledronic acid sequentially and 15 patients received zoledronic acid and ibandronate sequentially. Patients with MM routinely received pulse dexamethasone 40 mg for 4 days every 4 weeks as part of their treatment, whereas patients with solid tumors received corticosteroids only in association with taxane-based chemotherapy (on days −1, 0, and occasionally days 1 through 3 after treatment every 2 to 3 weeks).

Exposure to Bisphosphonates and Development of Osteonecrosis

The median number of bisphosphonate infusions administered to the whole population was 15 (range, six to 74) and median time of exposure was 20 months (range, four to 86 months). MM patients received a median of 23 infusions (range, six to 74 infusions), breast cancer patients received a median of 14.5 cycles (range, six to 56 cycles), prostate cancer patients received a median of 12 cycles (range, six to 56 cycles), and patients with other neoplasms received a median of 10 cycles (range, six to 21 cycles).

Seventeen patients (6.7%) were diagnosed with osteonecrosis of the jaw: 11 (9.9%) of 111 patients with MM, two (2.9%) of 70 with breast cancer, three (6.5%) of 46 with prostate cancer, and one (4%) of 25 with other neoplasms. There was no association of the development of osteonecrosis with primary site ($P = .289$), sex ($P = .258$), or age ($P = .247$). All occurrences of ONJ were diagnosed in patients who were treated with zoledronic acid either alone (seven patients; 6.7%) or after pamidronate (nine patients; 13%), or preceding ibandronic acid (one patient; 6.7%). The association of osteonecrosis with the type of bisphosphonate showed a marginal statistical significance ($P = .063$; Table 1). Among patients with MM, six (8.8%) of 68 patients who received

Table 1. Patient Characteristics

Characteristic	Osteonecrosis: Yes — No. of Patients	Osteonecrosis: Yes — %	Osteonecrosis: No — No. of Patients	Osteonecrosis: No — %	*P*
Sex					.258
Male	10	8.7	113	91.3	
Female	7	5.1	138	94.9	
Age, years					.247
Median	61		64		
Range	43-72		26-85		
Disease					.289
Breast cancer	2	2.9	68	97.1	
Multiple myeloma	11	9.9	100	90.1	
Prostate cancer	3	6.5	43	93.5	
Other	1	4	24	96	
Type of bisphosphonate					.063
Zoledronic acid	7	6.7	98	93.3	
Pamidronate	0	0	58	100	
Ibandronic acid	0	0	5	100	
Pamidronate + zoledronic acid	9	13	60	87	
Zoledronic acid + ibandronic acid	1	6.7	14	93.3	
Thalidomide use					.571
Yes	6	8.8	62	91.2	
No	5	12.2	38	87.8	
Time of exposure, months					
All patients					
Median	20				
Range	4-86				
Breast cancer					
Median	17.9				
Range	4-77.8				
Multiple myeloma					
Median	28.4				
Range	4.5-86				
Prostate cancer					
Median	14.4				
Range	4-66.5				
Other					
Median	10.7				
Range	4.4-47.3				
Zoledronic acid					
Median	16.6				
Range	4-53.5				
Pamidronate					
Median	13.7				
Range	4-82.4				
Ibandronic acid					
Median	6.5				
Range	5-21				
Pamidronate + zoledronic acid					
Median	40.2				
Range	9.4-86				
Zoledronic acid + ibandronic acid					
Median	16				
Range	7.5-49.1				

thalidomide and five (12.2%) of 43 patients who did not were diagnosed with osteonecrosis ($P = .571$).

Time of exposure to bisphosphonates was strongly associated with the development of ONJ (Table 2). No patient who received fewer than 13 treatments with bisphosphonates developed osteonecrosis. Patients who developed ONJ received a median number of 35 infusions (range, 13 to 68 infusions), whereas the respective number for patients

Table 2. Incidence of Osteonecrosis Related to Number of Infusions and Time to Exposure

Parameter	Osteonecrosis: Yes — No. of Patients	Yes — %	No — No. of Patients	No — %	*P*
Total No. of infusions	35		15		< .001
Range	13-68		6-74		
No. of infusions					< .001
6-12	0	0	101	100	
13-24	6	7.5	74	92.5	
25-36	3	7.9	35	92.1	
37-48	3	17.6	14	82.4	
49-60	4	36.4	7	63.6	
> 60	1	20	4	80	
Total months of exposure					
Median	39.3		19		< .001
Range	11-86		4-84.7		
Time of exposure, months					< .001
4-12	1	1.5	65	98.5	
13-24	4	4.3	88	95.7	
25-36	3	7.7	36	92.3	
37-48	2	7.7	24	92.3	
49-60	1	9.1	10	90.9	
> 60	6	33.3	12	66.7	

with no osteonecrosis was 15 infusions (range, six to 74 infusions; $P < .0001$). Median time of exposure to bisphosphonates was 39.3 months for patients with osteonecrosis (range, 11 to 86 months), compared with 19 months (four to 84.7 months) for patients with no osteonecrosis ($P = .001$).

Figure 1 shows the cumulative hazard of developing ONJ for the whole population. Table 3 shows the cumulative hazard at various time points after the initiation of treatment with bisphosphonates. The cumulative hazard increased above 1% after 12 months of treatment up to 11% at 4 years. In analyses of hazards according to treatment with thalidomide, no significant difference was evident in the respective rates ($P = .362$). There was also no significant difference according to the primary site (myeloma, breast, prostate, other; $P = .06$). For type of bisphosphonates administered (according to the grouping in Table 1), a significant difference in the respective hazards of developing ONJ was seen ($P = .003$). To further study this difference, we compared the cumulative hazard rates between patients who received zoledronic acid alone versus those who received pamidronate alone or with subsequent zoledronic acid. The hazard of developing ONJ was significantly higher in the zoledronic acid group ($P < .001$; Fig 2A). The hazard was 1% within the first year of treatment, increasing to 21% at 3 years for zoledronic acid, whereas the hazard among the other group was 0% for the first 2 years, increasing to only 7% after 4 years of treatment (Table 3).

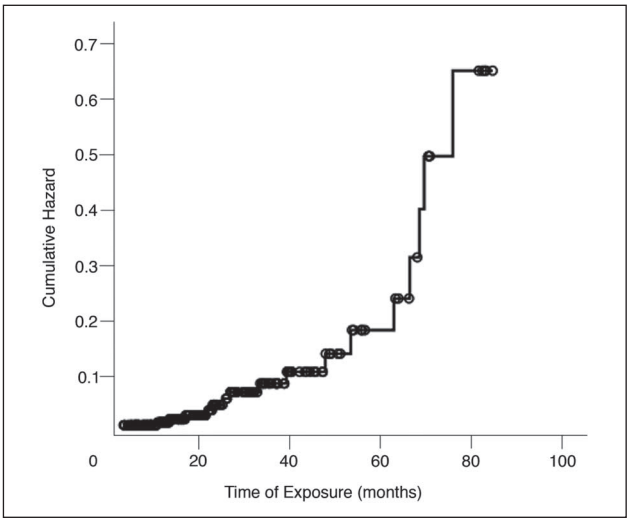

Fig 1. Cumulative hazard of developing osteonecrosis of the jaw from the date of initiation of treatment among 252 patients treated with bisphosphonates.

Given that time of exposure was different among patients with different primary sites or different type of bisphosphonates administered (Table 1), we also compared the hazards of developing ONJ between different levels of the indicated factors at 48 months post-treatment initiation. This time point was chosen according to the maximum time of exposure of the subgroup with the smallest range. Patients who received treatment beyond these points were censored, independently of whether they subsequently developed ONJ. There was no significant difference in the hazards between different primary sites ($P = .517$). On the contrary, the hazard was significantly higher in the zoledronic acid group compared with pamidronate alone or with subsequent zoledronic acid ($P = .005$; Fig 2B).

Characteristics and Management of Patients With ONJ

The characteristics of the 17 patients with osteonecrosis are summarized in Table 4. No patient had received radiation at the area of the head and neck. At the time of diagnosis of ONJ, three patients (17.6%) were receiving chemotherapy, two patients (12%) were receiving an aromatase inhibitor, and 10 patients (59%) were receiving corticosteroids, whereas two patients (12%) had received corticosteroids in the past. The remaining five patients (29%) had never received corticosteroids.

Fourteen patients had osteonecrosis of the mandible and three patients had osteonecrosis of the maxilla. In all patients pain was the presenting symptom, whereas patients who had prior dental extraction or artificial dentures had also purulent discharge. In two patients who had not had previous dental extraction or dentures, destabilization of their teeth occurred. In 13 patients dental extraction within the last year preceded the diagnosis of osteonecrosis, two patients had dentures, and two patients had no prior

Table 3. Cumulative Hazard of Developing Osteonecrosis of the Jaw *v* Duration of Treatment

Treatment	Cumulative Hazard							
	12 Months		24 Months		36 Months		48 Months	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
All (N = 252)	0		3	1 to 5	7	1 to 13	11	3 to 19
Zoledronic acid (n = 105)	1	0 to 3	7	1 to 13	21	3 to 39	21	3 to 39
Pamidronate/pamidronate and zoledronic acid (n = 127)	0		0		2	0 to 6	7	0 to 15

procedures in the oral cavity. Diagnosis was clinical in 11 patients, whereas biopsy was obtained in six patients to exclude metastatic disease. Necrotic bone was the only histologic finding, with surrounding bacteria but no evidence of bacterial invasion in the area of necrosis. Bisphosphonate infusions were discontinued after the confirmation of diagnosis. Management of all patients was conservative. Only minor debridement procedures were attempted to reduce sharp edges and trauma to surrounding tissues. All patients received multiple courses of antibiotics. The initial regimen contained amoxicillin or amoxicillin/clavulanate or metronidazole. Improvement of oral hygiene was recommended and oral rinses of chlorhexidine were prescribed. Measures were taken to reduce the contact of artificial dentures with the exposed bone.

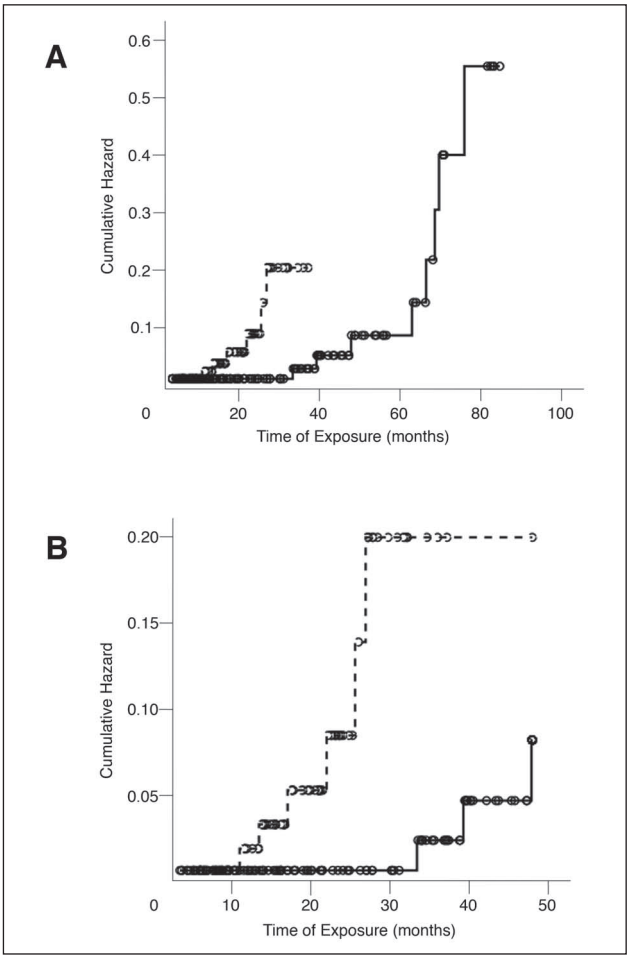

Fig 2. Cumulative hazard of developing osteonecrosis of the jaw according to treatment with zoledronic acid (– – – –) or pamidronate ± zoledronic acid (——) according to (A) time of exposure and (B) when patients receiving treatment for more than 48 months were censored irrespective of later development of osteonecrosis.

Treatment with antibiotics resulted in transient improvement, but only one patient showed sustained improvement of osteonecrosis after multiple courses of antibiotics. The other 16 patients had persistent disability, mainly consisting of recurrences with purulent discharge and pain after the discontinuation of the antibiotics. One patient received hyperbaric oxygen without improvement. The minimum follow-up after the development of osteonecrosis has been 4 months (range, 4 to 24 months) and the lack of symptomatic or radiologic improvement in these 16 patients indicates that bone defects are permanent.

DISCUSSION

Osteonecrosis refers to the death of the bone as a result of impaired blood supply to the affected areas. Cancer and its treatment have been described as risk factors for the development of osteonecrosis.[16] The most common site of osteonecrosis is the femoral head. Avascular ONJ has been associated predominantly with radiation of the head and neck, known as osteoradionecrosis,[17] but has also been described after chemotherapy.[18,19] Recently, ONJ has been reported after treatment with the bisphosphonates pamidronate and zoledronic acid in cancer patients.[8-15] Although these reports make the association of bisphosphonate and the development of ONJ likely, the true incidence of osteonecrosis is unknown. The first attempt to determine true incidence was reported by Durie et al,[10] who performed a Web-based survey in 1,203 patients with MM and breast cancer receiving bisphosphonates. Some limitations of the study include the fact that the diagnosis of ONJ was based on the answers given by the patients and that patients with dental problems might have been more responsive to the survey. We attempted to overcome this problem by prospectively studying the development of osteonecrosis during the last 2 years. This is the first

Table 4. Characteristics of Patients With Osteonecrosis

Sex	Disease	No. of Infusions	Site of Osteonecrosis	History of Corticosteroids	Use of Corticosteroids at Diagnosis	Dental Extraction	Chemotherapy at Diagnosis	Outcome of ONJ
F	Myeloma	52	Maxilla	Pulsed	Pulsed	Yes	No	Permanent disability
M	Myeloma	52	Mandible	No	No	Denture	No	Permanent disability
M	Renal	14	Mandible	No	No	Yes	No	Permanent disability
M	Prostate	35	Mandible	Yes	Yes	Yes	Yes	Permanent disability
M	Prostate	23	Mandible	Yes	Yes	Yes	Yes	Permanent disability
F	Myeloma	25	Mandible	No	No	Yes	No	Permanent disability
F	Breast	50	Maxilla	No	No	Yes	No	Permanent disability
M	Myeloma	69	Mandible	Pulsed	Pulsed	Denture	No	Permanent disability
M	Prostate	56	Mandible	Yes	Yes	Yes	Yes	Permanent disability
M	Myeloma	43	Mandible	Pulsed	Pulsed	Yes	No	Permanent disability
M	Myeloma	33	Maxilla	Pulsed	No	No	No	Permanent disability
M	Myeloma	23	Mandible	Pulsed	Pulsed	Yes	No	Permanent disability
F	Myeloma	17	Mandible	Pulsed	No	Yes	No	Improvement
F	Breast	13	Mandible	No	No	No	No	Permanent disability
F	Myeloma	42	Mandible	Pulsed	Pulsed	Yes	No	Permanent disability
F	Myeloma	16	Mandible	Pulsed	Pulsed	Yes	No	Permanent disability
M	Myeloma	21	Mandible	Pulsed	Pulsed	Yes	No	Permanent disability

Abbreviation: ONJ, osteonecrosis of the jaw.

analysis using this methodology; we believe this method overcomes some of the limitations of the previous reports and provides a denominator for the development of ONJ. Furthermore, our analysis is the first to include all types of cancer patients and thus provides the opportunity to assess possible differences among different primary sites. A limitation, common for all reports up to now, is its retrospective nature. Retrospective studies are subject to biases, the most important of which may have been introduced by the increased awareness of this adverse effect after 2003. We attempted to minimize that effect by selecting patients based on the time of exposure of patients with documented ONJ. We cannot exclude the possibility that a few patients before that time point may have been missed. Nevertheless, this number is likely to be small, given that ONJ causes intense symptoms, which cannot remain unrecognized.

The incidence of osteonecrosis in MM patients was 9.9% and the incidence in breast cancer patients was 2.9%, which are slightly different from those of Durie et al[10] for documented osteonecrosis (6.8% and 4.4%, respectively). The difference in the incidence between myeloma and breast cancer in our series is not significant and is most probably due to the different time of exposure between these groups. Indeed, our analysis indicated that the time of exposure to the drug and the number of infusions are the most significant risk factors for development of osteonecrosis. None of our patients who received fewer than 12 bisphosphonate infusions has developed ONJ, whereas the median exposure to the drug for patients who developed ONJ was almost twice that of patients who did not. Similar observations have been reported in abstract form by Durie et al.[20] Our analysis suggested a continuous increase in the incidence even after 5 years of exposure. Nevertheless, these results should be viewed with caution because of the small number of patients who have had such long exposure.

The type of bisphosphonate may play a role in the development of ONJ. This complication has been described exclusively after exposure to nitrogen-containing bisphosphonates pamidronate and zoledronic acid. Furthermore, Durie et al[10] suggested that the risk is higher with zoledronic acid than with pamidronate. The difference between the two types of bisphosphonates is even sharper in our study. We did not observe any occurrences of ONJ with pamidronate alone, although there were nine occurrences among 69 patients (13%) treated with pamidronate and zoledronic acid sequentially. The difference in the hazard between zoledronic acid and pamidronate plus or minus zoledronic acid was significant, indicating that the development of ONJ occurs earlier with treatment with zoledronic acid. The reason for this difference is unknown. A possible explanation is the more potent inhibitory effect of zoledronic acid on bone turnover compared with pamidronate. Pamidronate is approximately 100- to 700-fold more potent than etidronate, whereas ibandronate and zoledronic acid show 10,000- to 100,000-fold greater potency than etidronate.[21] Furthermore, zoledronic acid produced a greater reduction of collagen type-I degradation products (*N*-telopeptide) than pamidronate in a recent study,[22] confirming the stronger antiresorptive activity of zoledronic acid. Thus, we may assume that the continuous, potent decrease in bone turnover caused by zoledronic acid may lead to increased bone fragility in the long run and, in combination with other local factors that are present in the jaw, to the development of ONJ.

Impaired blood supply has been implicated in the development of ONJ.[23] There have been several reports indicating that zoledronic acid has antiangiogenic activity.[24-26]

This might explain its association with ONJ and the difference compared with pamidronate, the antiangiogenic properties of which are less established. We also studied the effect of thalidomide, an effective antimyeloma agent[27] with antiangiogenic properties. We found no association of thalidomide use with the development of ONJ.

None of our patients who received ibandronate alone developed osteonecrosis. Ibandronate has only been approved recently for bone metastases from breast cancer and, thus, a longer follow-up is required until its association with ONJ can be accurately assessed.

Apart from time of exposure and type of bisphosphonates, corticosteroids and chemotherapy have been implicated in the development of ONJ.[16,18,19,28] Most patients who developed osteonecrosis had been treated with one or both. Nevertheless, one patient with renal cancer had never received either corticosteroids or chemotherapy, whereas five patients had never received corticosteroids. Because of the diversity of the chemotherapy regimens and the timing of administration, it was impossible to perform an analysis addressing the contribution of this factor in the development of ONJ. Similarly, there was considerable diversity regarding the use of corticosteroids among the patients included in our study. The contribution of corticosteroids in the development of bisphosphonates-induced ONJ should be addressed in properly designed studies. It has been speculated that dental procedures may be the precipitating factor,[8,10,11] as indeed was the case for most of our patients. Nevertheless, no dental procedures or use of dentures were reported in two patients.

We conclude that ONJ is a complication that is correlated with long-term use of bisphosphonates; this complication has received much publicity and developed much controversy recently.[29,30] This might have implications in the current standards of use of these drugs in cancer patients. The American Society of Clinical Oncology guidelines for MM[31] and breast cancer[32] suggest that bisphosphonates should be administered "until there is evidence of a substantial decline in the patient's general performance status." Taking into consideration the natural history of these diseases, this could result in administration of bisphosphonates to some patients for several years. Nevertheless, the studies on which current guidelines were based usually administered bisphosphonates for a maximum of 2 years.[7,33-35] In view of the data reported by us as well as by others,[10,15,19] caution is required for use of pamidronate and zoledronic acid beyond 2 years. Furthermore, patients should improve their oral hygiene, whereas oncologists and dentists should be aware of this complication and its management. This is also emphasized by new postmarketing guidelines issued for pamidronate and zoledronic acid.[36] Reinitiating bisphosphonate therapy in patients suffering from osteonecrosis is debated and warrants additional study. Prospective randomized studies are needed to assess the incidence of ONJ and the safety of bisphosphonates in cancer patients.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Meletios A. Dimopoulos			Novartis (A)		Celgene (A); Sanofi (A)			
Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required								

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