The Oncologist®

Symptom Management and Supportive Care

Osteonecrosis of the Maxilla and Mandible in Patients with Advanced Cancer Treated with Bisphosphonate Therapy

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Key Words. Bisphosphonate therapy • Pamidronate • Zoledronic acid • Osteonecrosis of the jaw

Disclosure: C.L.E. is a participating investigator in a Novartis-sponsored zoledronic acid trial, CZOL446E2352. C.H.V.P. has served as a consultant for Amgen and Roche and is a participating investigator in a Novartis-sponsored zoledronic acid trial, CZOL446E2352. J.M.H. is a consultant to Novartis and a member of the Data Monitoring Committee for the zoledronic acid trial CZOL446E2352. A.F. is on the speaker's bureau for Novartis. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or staff managers.

ABSTRACT

Cases of osteonecrosis of the jaw (ONJ) have been reported with an increasing frequency over the past 5 years. ONJ is most often identified in patients with cancer who are receiving intravenous bisphosphonate (IVBP) therapy, but it has also been diagnosed in patients receiving oral bisphosphonates for nonmalignant conditions. To further categorize risk factors associated with ONJ and potential clinical outcomes of this condition, we performed a retrospective study of patients with metastatic bone disease treated with intravenous bisphosphonates who have been evaluated by the Memorial Sloan-Kettering Cancer Center Dental Service between January 1, 1996 and January 31, 2006. We identified 310 patients who met these criteria. Twenty-eight patients were identified as having ONJ at presentation to the Dental Service and an additional 7 patients were subsequently diagnosed with ONJ. Statistically significant factors associated with increased likelihood of ONJ included type of cancer, duration of bisphosphonate therapy, sequential IVBP treatment with pamidronate followed by zoledronic acid, comorbid osteoarthritis or rheumatoid arthritis, and benign hematologic conditions. Our data do not support corticosteroid use or oral health as a predictor of risk for ONJ. Clinical outcomes of patients with ONJ were variable with 11 patients demonstrating improvement or healing with conservative management. Our ONJ experience is presented here. ***The Oncologist*** 2008;13:911–920

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1083-7159/2008/$30.00/0 doi: 10.1634/theoncologist.2008-0091

Introduction

Many cancers in their advanced stages involve the bone (metastatic bone disease). Bone metastases are associated with significant morbidity and mortality, including fracture, hypercalcemia of malignancy, spinal cord compression, and the need for surgery or radiation to bone [1]. These events are often collectively termed skeletal related events (SREs). Bisphosphonates are chemical compounds that inhibit osteoclast activity. Clinically relevant bisphosphonates for cancer treatment include clodronate, ibandronate, pamidronate, and zoledronic acid. However, only pamidronate and zoledronic acid are approved by the U.S. Food and Drug Administration for the treatment of osseous tumor involvement. Randomized controlled clinical trials investigating bisphosphonate therapy have demonstrated a decrease in the risk for an SRE by approximately one third. Hence, bisphosphonate therapy has been incorporated into the therapy of patients with metastatic bone disease [2].

In 2003, investigators, including our group, reported an apparent association between bisphosphonate use and the oral syndrome of osteonecrosis of the jaw (ONJ), where necrotic bone is exposed [3–7]. ONJ is frequently associated with pain and superinfection. This syndrome has subsequently been reported with increasing frequency in the dental and medical literature. The incidence of ONJ in patients with cancer receiving bisphosphonate therapy for metastatic bone disease has been estimated to be in the range of 1%–10%, but the true incidence of ONJ in patients with or without cancer is unknown [8]. We herein present a retrospective study of the association between patient, tumor, and dental characteristics and the development of ONJ in patients evaluated in the dental clinic at a tertiary cancer center following i.v. bisphosphonate (IVBP) therapy.

Patients and Methods

Following approval by the Memorial Sloan-Kettering Cancer Center (MSKCC) Institutional Review Board, patients treated with IVBP therapy were identified through MSKCC's pharmacy database. We performed a retrospective chart review of patients with a history of multiple myeloma (MM), breast cancer (BC), or prostate cancer (PC) who received IVBP therapy at MSKCC and were evaluated by the MSKCC Dental Service between January 1, 1996 and January 31, 2006. Using the pharmacy database and the medical/dental records, patients treated with IVBP therapy before their first dental visit were identified and categorized based on their ONJ status at their first dental visit. ONJ was defined as exposed bone in the maxilla or mandible without evidence of tumor involvement and without prior irradiation of the affected site to a dose $>$5,500 cGy. An exposed jaw bone in an area previously treated with $\geq$5,500 cGy represents osteoradionecrosis, a complication of head and neck cancer radiotherapy that is a separate entity from ONJ. The study dates of 1996–2006 were selected as they permitted the integration of the multidisciplinary records associated with patient care (pharmacy, medical, and dental records). The study definition of ONJ permits reliable abstraction of data using an interdisciplinary approach. Hence, we used this ONJ definition to look back in time as far as the record systems were integrated (1996).

The primary objective of the study was to investigate the association between clinical and pathologic factors and ONJ development. The ONJ status at the time of the first dental evaluation was used to define the cohorts in this analysis. ONJ lesions were retrospectively staged according to the system proposed by Ruggiero et al. [9]. Patient, tumor, and dental characteristics were investigated for an association with the risk for ONJ development in our population of patients; those who developed ONJ (ONJ^+) were compared with those who did not develop ONJ (ONJ^-). Information extracted from the MSKCC health care records and pharmacy database included demographics, primary cancer diagnosis, type and duration of IVBP treatment, social history, comorbid conditions, type of antineoplastic therapy, history of corticosteroid therapy, and dental health. The duration of IVBP treatment was defined as the length of IVBP treatment before an ONJ diagnosis for the ONJ^+ patients and the length of IVBP treatment before the first dental visit for the ONJ^- patients.

The associations between the different patient characteristics, tumor variables, and dental variables and the development of ONJ were examined using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. p-values <0.05 were considered statistically significant.

The secondary objectives of this study were to describe the clinical features, management, and outcome of ONJ in the cohort of patients who had ONJ before/at the first dental visit and those who developed ONJ after the first dental visit.

Results

Demographics

In total, 4,835 patients were treated with IVBP therapy at MSKCC in the study time period, of whom 310 were referred to the Dental Service by their medical oncologists for evaluation and management of various oral and dental complaints including ONJ and other oral lesions as well as dental caries and periodontal disease. Of the 310 patients who received IVBP treatment prior to their first MSKCC dental visit, 28 had ONJ (ONJ^+) and 282 did not.

The median dental follow-up of the 310 patients was 8 months (range, 0–39 months). Dental follow-up was defined as the time between the first and last dental visits. As would be expected by the study period, most patients had been exposed to pamidronate; there were 169 patients (54.5%) who had received pamidronate as their only IVBP, 77 (24.8%) received zoledronic acid alone, and 64 (20.7%) had a history of sequential treatment with pamidronate and zoledronic acid. At the time of the first dental visit, the median length of IVBP treatment was 11.6 months (range, 0.1–105.7 months). In the ONJ^+ cohort, the median bisphosphonate therapy duration was 28.8 months (range, 0.9–100.8 months). Figure 1 illustrates the distribution of the duration of IVBP treatment before ONJ/the first dental visit among the ONJ^+ and ONJ^- cohorts.

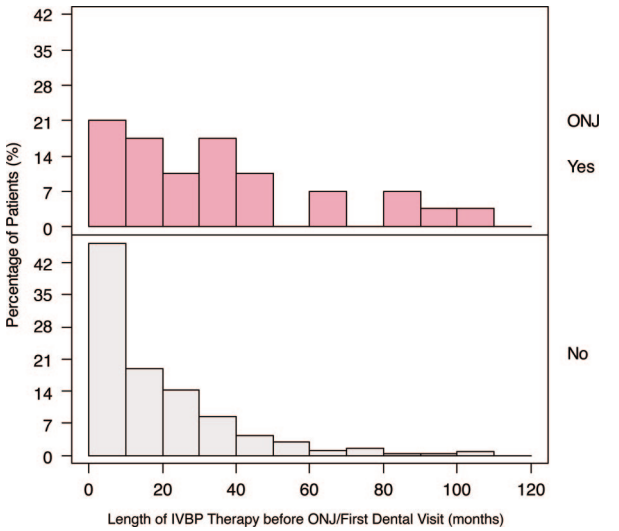

Figure 1. IVBP therapy duration prior to ONJ diagnosis/first dental visit in ONJ^+ ($n = 28$) and ONJ^- ($n = 282$) patients.

Abbreviations: IVBP, i.v. bisphosphonate; ONJ, osteonecrosis of the jaw; ONJ^+, ONJ present at the first dental visit; ONJ^-, ONJ not present at the first dental visit.

Association Between Patient, Treatment, and Dental Parameters and ONJ Development

Table 1 depicts factors univariately associated with the development of ONJ. Development of ONJ had a positive statistically significant association with a primary cancer diagnosis of BC, sequential IVBP treatment with pamidronate followed by zoledronic acid, the duration of IVBP treatment, rheumatoid/osteoarthritis, and a nonmalignant hematologic disorder (e.g., anemias, thalassemias, sickle-cell trait/disease, coagulation defects). A negative association was identified with exposure to 5-fluorouracil, cyclophosphamide, doxorubicin, methotrexate, corticosteroids, and antiangiogenic agents (e.g., bevacizumab, bortezomib, and thalidomide). The occurrence of dental caries was also found to be negatively associated with ONJ development. Periodontal disease and oral hygiene were not found to be associated with ONJ development.

Clinical Characteristics of ONJ

The clinical features of the 35 patients who had ONJ at their first dental visit or developed ONJ after their first dental visit are summarized in Table 2. In all cases, the exposed bone appeared nonvital, and on being probed was asymptomatic, confirming the necrotic nature of the bone. The surrounding soft tissues were typically erythematous and inflamed. The ONJ lesions at initial presentation varied in size, with most ($n = 25$, 71.4%) of the lesions measuring 1–5 mm in diameter while the rest were >1 cm in diameter. Twenty-two (62.9%) were symptomatic, with the most common complaints being pain and/or numbness in the affected area, soft tissue swelling, drainage, and tooth mobility. One patient developed a draining neck fistula corresponding to the site of ONJ. Two patients developed a jaw fracture associated with ONJ. The ONJ lesions in three (8.6%) of the patients were loose and became progressively mobile over time; these lesions measured at least 1 cm. A slight majority of the patients ($n = 18$, 51.4%) had a previous nonhealing dental surgical procedure in the ONJ site. Spontaneous ONJ was identified in 14 (40%) patients and occurred in the posterior lingual mandible or the area of the mylohyoid ridge. The mandible was the more common location, being noted in 21 (60%) patients, with 12 (34.3%) in the maxilla and the rest in both arches.

Radiographic Characteristics of ONJ

Dental radiographs were available for review in 94% ($n = 33$) of the patients. Radiographic findings in the area of ONJ ranged from relatively normal bony trabeculation, diffuse radiolucent areas indicating incomplete bony healing in an area of previous dental surgery, to focal areas of radiolucency, bony sequestrum, "mothy bone," or lytic changes. Small areas (<1 cm) of nonprogressing ONJ often had normal findings on panoramic radiographs. Likewise, computed tomography scans showed lytic changes and bony destruction in those with larger (>1 cm) ONJ lesions. Bone scans, obtained for clinical indications, were available for review in 16 (45.7%) patients and showed increased uptake in the ONJ site in 62.5% ($n = 10$ of 16) of the cases (Fig. 2).

Histologic Characteristics of ONJ

Thirteen (37.1%) patients underwent conservative bone biopsy or removal of sharp bony spicules in the area of ONJ. In all of the 13 bone tissue samples, histological examination demonstrated fragments of necrotic bone associated with florid bacterial colonization morphologically

Table 1. ONJ development and its association with various factors

	All patients (%)	ONJ[+a]	ONJ[−b]	*p*-value
n	310	28 (9.0 %)	282 (91.0)	
Primary diagnosis				
Breast cancer	134 (43.2)	18 (64.3)	116 (41.1)	.01
Multiple myeloma	145 (46.8)	6 (21.4)	139 (49.3)	
Prostate cancer	31 (10.0)	4 (14.3)	27 (9.6)	
BP				
Pamidronate (P)	169 (54.5)	4 (14.3)	165 (58.5)	
Zoledronic acid (Z)	77 (24.8)	10 (35.7)	67 (23.8)	
P + Z	64 (20.7)	14 (50.0)	50 (17.7)	<.001
Length of BP treatment (mos) before ONJ/first dental visit				
Mean (median)	19.3 (11.6)	34.1 (28.8)	17.8 (11.1)	
Range	0.07–105.7	0.9–100.8	0.07–105.7	.001
Rheumatoid arthritis/osteoarthritis				
Yes	21 (6.8)	9 (32.1)	12 (4.3)	<.001
No	289 (93.2)	19 (67.9)	270 (95.7)	
Hematologic disease[c]				
Yes	8 (2.6)	5 (17.9)	3 (1.1)	<.001
No	302 (97.4)	23 (82.1)	279 (98.9)	
5-Fluorouracil				
Yes	59 (19.0)	0 (0)	59 (20.9)	
No	251 (81.0)	28 (100)	223 (79.1)	.004
Cyclophosphamide				
Yes	182 (58.7)	5 (17.9)	177 (62.8)	
No	128 (41.3)	23 (82.1)	105 (37.2)	<.001
Doxorubicin				
Yes	160 (51.6)	7 (25)	153 (54.3)	
No	150 (48.4)	21 (75)	129 (45.7)	.005
Methotrexate				
Yes	52 (16.8)	0 (0)	52 (18.4)	
No	258 (83.2)	28 (100.0)	230 (81.6)	.007
Corticosteroid				
Yes	261 (84.2)	18 (64.3)	243 (86.2)	
No	49 (15.8)	10 (35.7)	39 (13.8)	.01
Antiangiogenic agent				
Yes	74 (23.9)	2 (7.1)	72 (25.5)	
Bevacizumab	7	0	7	
Bortezomib (B)	7	0	7	
Thalidomide (T)	40	2	38	
B + T	20	0	20	
No	236 (76.1)	26 (92.9)	210 (74.5)	.034
Dental caries				
Yes	173 (55.8)	7 (25.0)	166 (58.9)	
No	119 (38.4)	20 (71.4)	99 (35.1)	<.001
NA[d]	18 (5.8)	1 (3.6)	17 (6.0)	

(continued)

Table 1. (Continued)

	All patients (%)	ONJ^{+a}	ONJ^{-b}	*p*-value
Periodontal disease[e]				
Yes	260 (83.9)	24 (85.7)	236 (83.7)	.64
No	15 (4.8)	2 (7.1)	13 (4.6)	
NA[d]	35 (11.3)	2 (7.1)	33 (11.7)	
Presence of symptomatic periodontally compromised teeth[f]				
Yes	72 (23.2)	4 (14.3)	68 (24.1)	.25
No	210 (67.7)	23 (82.1)	187 (66.3)	
NA[d]	28 (9.0)	1 (3.6)	27 (9.6)	
Oral hygiene				
Excellent	6 (1.9)	0 (0)	6 (2.1)	.96
Good	78 (25.2)	8 (28.6)	70 (24.8)	
Fair	142 (45.8)	14 (50.0)	128 (45.4)	
Poor	73 (23.6)	6 (21.4)	67 (23.8)	
NA[d]	11 (3.6)	0 (0)	11 (4.0)	

[a]ONJ present at first dental visit.
[b]ONJ not present at first dental visit.
[c]Hematologic disease: conditions including anemias, thalassemias, sickle-cell trait/disease, coagulation defects.
[d]NA: not applicable; data are missing in medical/dental records.
[e]Periodontal disease: no: no evidence of radiographic crestal alveolar bone loss; yes: at least 25% radiographic crestal alveolar bone loss.
[f]Symptomatic periodontally compromised teeth: yes: pain, tooth mobility, gingival swelling, purulent discharged in areas with at least 25% radiographic crestal alveolar bone loss; no: absence of above symptoms in areas with at least 25% radiographic alveolar bone loss.
Abbreviations: BP, bisphosphonate; ONJ, osteonecrosis of the jaw.

consistent with *Actinomyces* spp. No macrobacterial cultures were available for our review. Although the bony trabeculae in each specimen appeared jagged and "moth-eaten," associated osteoclasts were generally not observed in the affected bone. No metastatic tumor was identified. Soft tissue biopsy consistently revealed inflamed squamous mucosa or granulation tissue, but none showed any evidence of malignancy (Fig. 3).

Outcome

Resolution of ONJ was defined as complete soft tissue coverage without symptoms and without clinical evidence of exposed bone, and occurred in three patients. In these three patients, IVBP therapy was discontinued in one and remain unchanged in the other two patients. In the patient in whom IVBP therapy was discontinued, complete resolution of the maxillary ONJ site occurred after the bone lesion became increasingly mobile and ultimately exfoliated 2 years following the first dental visit. The underlying tissue appeared healthy without apparent oroantral communication (Fig. 4). In the other two patients with ONJ resolution, the ONJ lesion resolved after 1 month in one patient (with a history of 35 months of pamidronate for MM) and after 25 months in the other (with a history of 64 months of pamidronate and zoledronic acid for metastatic BC). In eight patients, the ONJ site remained stable and unchanged (range of dental follow-up, 0–27 months), while 13 others had progression of ONJ (range of dental follow-up, 3–26 months). Progression constituted the development of new symptoms, the development of ONJ at another site, or an increase in the size of the ONJ with or without symptoms. Seven patients succumbed to their cancer during the study period and four were lost to follow-up.

Discussion

Among the cohort of 310 patients evaluated by the MSKCC Dental Service, 28 patients had ONJ at their first dental visit and seven patients developed ONJ thereafter. In order to most accurately examine the incidence of ONJ, the cohort must include all patients treated with IVBP therapy in the same time period. Because the dental cohort represents $<$10% of the total 4,835 cohort of patients who received IVBP therapy at our institution, the incidence of ONJ cannot be precisely determined. Furthermore, the accuracy of our estimates is limited by the retrospective study design. However, we can predict that the incidence of ONJ in patients with MM, BC, and PC treated with IVBP therapy at MSKCC is at least 0.72% (35 of 4,835).

Table 2. Clinical features of ONJ

Characteristic	All patients (%)	ONJ[+a]	ONJ[−→+b]
n	35	28 (80%)	7 (20)
Median (range) duration of BP treatment, mos[c]	26 (1–101)	26 (1–101)	19 (3–55)
Nature of ONJ			
Dental extraction/dental implant placement	18 (51.4)	14 (50.0)	4 (57.1)
Spontaneous	14 (40.0)	11 (39.3)	3 (42.9)
Both	3 (8.6)	3 (10.7)	0
Location of ONJ			
Maxilla	12 (34.3)	10 (35.7)	2 (28.6)
Mandible	21 (60.0)	16 (57.1)	5 (71.4)
Both	2 (5.7)	2 (7.1)	0
Anterior versus posterior			
Anterior	2 (5.7)	1 (3.6)	1 (14.3)
Posterior	32 (91.4)	26 (92.9)	6 (85.7)
Midline torus	1 (2.9)	1 (3.6)	0
Symptomatology			
Present	22 (62.9)	19 (67.9)	3 (42.9)
Absent	13 (37.1)	9 (32.1)	4 (57.1)
Size of exposed bone			
<1 cm	25 (71.4)	18 (64.3)	7 (100)
>1 cm	10 (28.6)	10 (35.7)	0
Clinical staging			
Stage 1	20 (57.1)	17 (60.7)	3 (42.9)
Stage 2	13 (37.1)	9 (32.1)	4 (57.1)
Stage 3	2 (5.7)	2 (7.1)	0
Bone scan available			
Yes	16 (45.7)	15 (53.6)	1 (14.3)
No	19 (54.3)	13 (46.4)	6 (85.7)
Management			
Antibiotic therapy	16 (45.7)	15 (53.6)	1 (14.3)
Conservative sequestrectomy/curettage	7 (20.0)	6 (21.4)	0
Chlorhexidine rinse 0.12%	35 (100.0)	25 (89.3)	6 (85.7)
Conservative bone biopsy	13 (37.1)	12 (42.9)	1 (14.3)
Outcome			
Resolution	3 (8.6)	2 (7.1)	1 (14.3)
No change in ONJ status	8 (22.9)	7 (25.0)	1 (14.3)
Progression of ONJ	13 (37.1)	11 (39.3)	2 (28.6)
Deceased	7 (20.0)	5 (17.9)	2 (28.6)
Lost to follow-up	4 (11.4)	3 (10.7)	1 (14.3)
Median dental follow-up (range)	15 (0–62)	4 (0–32)	5 (1–30)

[a]ONJ present at first dental visit.
[b]ONJ developed after first dental visit.
[c]Median duration of BP treatment at time of ONJ diagnosis.
Abbreviations: BP, bisphosphonate; ONJ, osteonecrosis of the jaw.

Risk factors associated with the development of ONJ were examined by association checking analysis and demonstrated a significant positive association between ONJ development and a primary cancer diagnosis of BC, se-

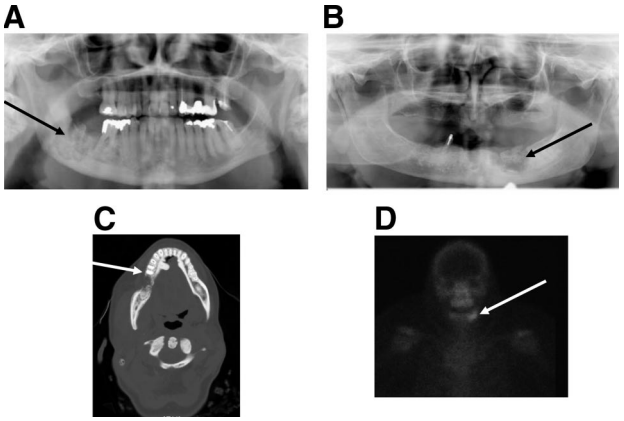

Figure 2. Radiographic characteristics of ONJ. **(A):** Panoramic radiograph of a nonhealing extraction socket showing progressive bony destruction in the right mandible (arrow). **(B):** Panoramic radiograph of spontaneous ONJ showing bony sequestrum in the left mandible (arrow). **(C):** Axial view of a computed tomography scan demonstrating a lytic lesion in the right body of the mandible (arrow). **(D):** Anterior view of bone scan showing increased uptake in the left mandible (arrow).

Abbreviation: ONJ, osteonecrosis of the jaw.

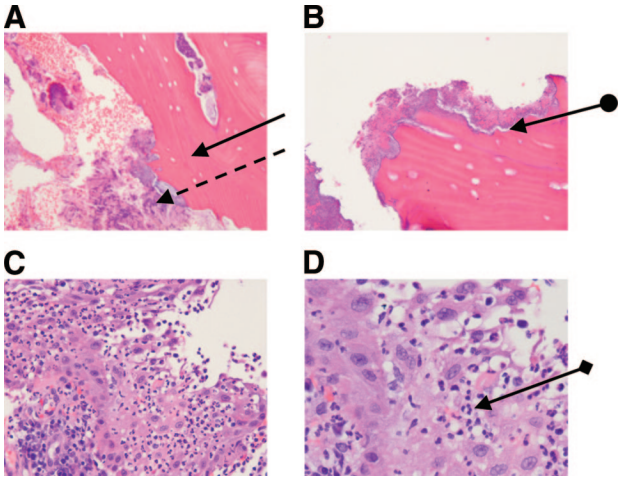

Figure 3. Histologic characteristics of ONJ. **(A):** Mandibular bone biopsy showing necrotic bone (solid arrow) with associated filamentous bacterial colonies morphologically resembling *Actinomyces israelli* (dashed arrow) (100× magnification). **(B):** The "moth-eaten" (oval arrow) appearance of the bone suggests that the *Actinomyces* bacteria's role in this process may be pathogenic (200× magnification). **(C):** Mandibular gingiva biopsy revealing acute inflammation (200× magnification). **(D):** At high power, polymononuclear neutrophils are evident (diamond arrow) (400× magnification). All specimens were stained with hematoxylin and eosin.

Abbreviation: ONJ, osteonecrosis of the jaw.

quential therapy with pamidronate and zoledronic acid, the length of IVBP therapy, rheumatoid arthritis and osteoarthritis, and a nonmalignant hematologic disorder. Our cohort demonstrated a significant negative association with exposure to 5-fluorouracil, cyclophosphamide, doxorubicin, and methotrexate. These findings are provocative in that patients with a history of BC appear to be at greater risk for ONJ, yet drugs commonly used in the treatment of BC (doxorubicin, cyclophosphamide, 5-fluorouracil, methotrexate) were identified as negative predictors of ONJ risk. One explanation regarding the relatively higher incidence of ONJ among BC patients is the fact that BC patients have a relatively longer life expectancy; hence, their lengths of bisphosphonate treatment time are longer and their likelihood of exposure to sequential pamidronate followed by zoledronic acid is higher. Our findings are consistent with those of others, in which the risk for ONJ in patients with metastatic cancer is in the range of approximately 1%–10% [10–12]. However, because of the retrospective nature of and the small number of cases in our study, the relationship between these confounding factors cannot be fully explored. Of note, our analysis indicated a negative association between ONJ and exposure to corticosteroid therapy.

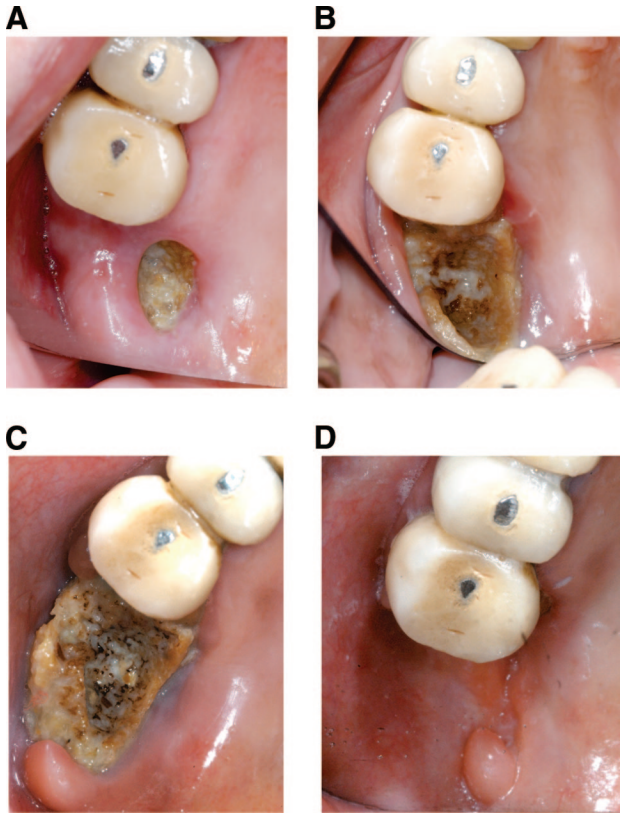

Figure 4. Clinical characteristics of ONJ. **(A):** First dental visit. The maxillary right molar tooth was extracted 1 year prior. The patient complained of drainage from the area of exposed bone. **(B):** Six months following the first dental visit. The size of the ONJ has increased. **(C):** One year following the first dental visit. The size of the ONJ continues to grow. **(D):** The exposed bone gradually became mobile and subsequently exfoliated 1 year later.

Abbreviation: ONJ, osteonecrosis of the jaw.

Although steroid use has long been associated with osteonecrosis of the long bones, the role of corticosteroids in the pathogenesis of osteonecrosis is unclear [13]. Steroids are routinely incorporated into anticancer therapeutic regimens and may be administered i.v. or orally. The retrospective nature of our investigation, like that of others, is limited in its ability to capture prescriptions filled in the outpatient setting. ONJ occurred in patients with good oral hygiene and in the absence of underlying dental or periodontal disease. Our data do not demonstrate a higher risk for ONJ in association with poor oral hygiene or the presence of periodontal disease. Our finding is contrary to the hypothesis that poor oral health (i.e., poor oral hygiene, presence of dental infection) is a risk factor for the development of ONJ [11]. An ongoing and planned prospective study will validate or refute this provocative finding. The outcome of ONJ in our cohort was variable, with only three patients demonstrating resolution of ONJ. In our experience, and that of others [15, 19], withholding or decreasing IVBP therapy did not appear to alter the course of ONJ.

In all bone biopsies in our study, florid bacterial colonization was present, with filamentous bacteria morphologically consistent with *Actinomyces*. In their histopathological study of 45 patients with actinomycosis of the jaws in which 26 patients had bisphosphonate-associated ONJ, Hansen et al. [14] found *Actinomyces* in direct contact with bone tissue. In addition, mixed inflammatory infiltrates with variable amounts of osteoclasts were typically found in the surrounding medullary spaces. It is currently unclear whether *Actinomyces* is actively contributing to ONJ development or progression or is simply an "innocent bystander"/secondary phenomenon related to the necrotic bone and anaerobic environment. Ongoing prospective studies are analyzing the bacterial component in gingival crevicular fluid in order to identify potential risk factors for ONJ development.

Our data showed that, among the ONJ^+ patients, the duration of IVBP therapy before ONJ onset was shorter for those receiving zoledronic acid (median, 8.7 months) than for those receiving pamidronate alone (median, 44.5 months) or pamidronate plus zoledronic acid (median, 31.5 months). This finding is consistent with other reports [3, 15–19]. This may be explained by zoledronic acid's considerably higher potency compared with pamidronate [19]. Of the 28 ONJ^+ patients, 20 had a $>$12-month history of IVBP therapy. Naturally, these patients were also exposed to other antineoplastic and supportive medications during this time frame as well. In our study, there were no definitive radiographic or histologic pathognomonic findings of ONJ. In all cases, the diagnosis of ONJ was made based on clinical assessment. Panoramic radiographs in our patients were nonspecific and nondiagnostic, which is consistent with the imaging findings of other investigators. In their study of patients treated with bisphosphonates who underwent bone scans, O'Connor et al. [20] found that jaw uptake on bone scan was not a reliable predictor of ONJ development. There was jaw uptake in 92% (12 of 13) of patients with ONJ and 70% (128 of 183) of patients with no ONJ. The difference was not significant between the two groups. However, other investigators have suggested that bone scans may be able to identify ONJ precursor lesions (Landesberg R, personal communication, [22]).

In our experience, approximately 60% of ONJ cases with bone scans available for review showed increased uptake in the ONJ site. This is a provocative finding given the assumption that necrotic bone would show no radiotracer uptake. However, radiotracer uptake on bone scan is a function of local perfusion and osteoblast activity. The noted increased uptake in ONJ may not occur in the necrosis, but as a reactive change in the surrounding bone. The resolution of the planar whole body bone scans, even when "spot views" of the head/jaw were obtained, was too poor to distinguish between the site of necrosis and adjacent or intermixed normal bone. In addition, on planar images, there is overlap of the site of necrosis and surrounding bone (two-dimensional image of a three-dimensional structure). While our data may not be definitive, they may serve as potential background data for future studies and aid the clinician in appreciating the protean findings associated with ONJ. Thus, we continue to search for reliable diagnostic and imaging techniques with which to assess and diagnose ONJ.

There is growing and intensive preclinical evidence showing that bisphosphonates may exert an antitumor effect on MM, BC, and PC through inhibition of angiogenesis [22–25]. Angiogenesis is an essential step in tumorigenesis [26]. It also plays an important role in wound healing and bone remodeling [27, 28]. Could an antiangiogenic effect of bisphosphonate therapy contribute to the development of ONJ? In our study, 74 patients were treated with the antiangiogenic agents bevacizumab, bortezomib, and thalidomide. However, out analysis showed a negative association between the use of these agents and ONJ development. The date from Aragon-Ching et al. [29] demonstrating a 17% incidence of ONJ in patients with PC receiving thalidomide, bevacizumab, docetaxel, and prednisone in a clinical trial (zoledronic acid was used as per standard practice) suggested that the risk for ONJ may be higher with chemotherapy regimens that include steroids and antiangiogenic agents. The high rate of ONJ identified in this prospective clinical study is provocative given the use of novel therapies; updated results are eagerly awaited.

Given the increasing reports of bisphosphonate-associ-

ated ONJ and the fact that the indications for bisphosphonate therapy are now expanding beyond the management of tumor-associated bone diseases to include benign metabolic bone diseases, clinicians and patients should be fully aware of ONJ as a possible treatment-related complication. ONJ guidelines have been generated by dental, medical, and bone societies [17, 30–33]. The National Institute for Dental and Craniofacial Research has generated a research-funding mechanism to investigate ONJ, and clinical trials investigating drugs that inhibit osteoclast function and/or activity have incorporated dental assessments and evaluation of ONJ into the clinical trials. The Southwest Oncology Group will be launching a prospective registry of patients with metastatic bone disease treated with IVBP therapy (S0702) and the German ONJ registry set up in 2004 now contains data on 600 patients (http://www.nyas.org). Prospective clinical and translational studies are clearly needed to investigate the pathogenesis of ONJ, to identify the risk factors for its development, and to develop means for its detection and management.

ACKNOWLEDGMENTS

A portion of this study was presented at various dental and medical scientific meetings.

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