INCIDENCE AND RISK FACTORS OF BISPHosphONATE-ASSOCIATED OSTEONECROSIS OF THE JAWS

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Abstract: Background. Intravenous bisphosphonate therapy has been used for treatment of benign and malignant bone diseases and has been linked to osteonecrosis of the jaws.

Methods. Records of 638 patients treated with intravenous bisphosphonates were reviewed. Drug used, number of infusions, dosing interval, dosage, duration, and occasion of osteonecrosis, diagnosed by history and physical examination, were analyzed.

Results. The overall incidence of osteonecrosis was 0.94% (6/638). No significant relationship was observed between the incidence of osteonecrosis and demographic parameters, primary tumor, cumulative drug dose, or dosing interval. However, patients who developed osteonecrosis had a significantly greater mean number of infusions (p = .016) and significantly greater mean hours of infusion time (p = .0036).

Conclusions. The findings suggest positive correlation between the development of osteonecrosis and drug exposure as measured by number of infusions and total infusion hours. However, the relatively low incidence of osteonecrosis precluded definition of a direct dose-response relationship.

Keywords: bisphosphonate; osteonecrosis; mandible; maxilla; incidence

Intravenous bisphosphonate therapy has been used to treat many benign and malignant diseases of the bones. This class of drugs can stabilize bone loss caused by osteoporosis, malignant bony metastasis, and multiple myeloma.1 Bisphosphonates pamidronate and zoledronic acid, act at sites of active bone remodeling by binding to hydroxyapatite, inhibiting osteoclast development and migration, and inducing osteoclast cell death, thereby decreasing bone resorption without affecting bone mineralization.2 Osteonecrosis of the mandible and maxilla has been increasingly reported as a complication of these medications.3–6 Package inserts for pamidronate and zoledronic acid were updated in 2003 to include information on bisphosphonate-associated osteonecrosis in the Precautions and Adverse Reactions sections.7 Despite heightened awareness through case reports and case series, understanding of risk factors and dose association is still limited. Although a few patients may present with no history of dental complaints, the majority of patients affected by bisphosphonate-associated osteonecrosis have been noted to have a history of dental comorbidity or dental procedures.3–5,8–11 We undertook this study to establish the incidence of and to identify
the risk factors for osteonecrosis developing in patients treated with intravenous bisphosphonate therapy.

PATIENTS AND METHODS

A retrospective review was conducted of all patients treated with intravenous bisphosphonate therapy at the University of Tennessee Cancer Institute between January 1, 2000, and April 1, 2006, to determine the incidence of osteonecrosis of the maxilla or mandible. The diagnosis of bisphosphonate-associated osteonecrosis was established by clinical and radiological evaluation in patients presenting with bone exposure and associated symptoms such as pain and swelling. All patients receiving intravenous pamidronate (Aredia, Novartis Pharmaceuticals, Basel, Switzerland), zoledronic acid (Zometa, Novartis Pharmaceuticals, Basel, Switzerland), or both agents with a malignant neoplasm were included in this cohort. However, any patients with a prior history of radiation to the head and/or neck were excluded. The study was approved by the University of Tennessee Institutional Review Board.

Data collected from patient records included age, sex, pertinent past medical history, underlying diagnosis, bisphosphonate used, number of chemotherapy infusions, chemotherapy dose, time interval between infusions, duration of infusion, cumulative dose, presenting signs and symptoms, and management.

The incidence of osteonecrosis was analyzed as a function of age, sex, primary tumor characteristics, and bisphosphonate dosing. Student’s t test, chi-square, and 1-way analysis of variance (ANOVA) were applied, where appropriate, and a p value less than .05 was considered statistically significant.

RESULTS

The study population included 638 consecutive patients treated with intravenous bisphosphonate therapy. The incidence of osteonecrosis of the mandible or maxilla was 0.94% (6 of 638 patients). Patient demographics are summarized in Table 1. Mean age of the study group was 67 years, and 61% were women. The most common primary malignancies included cancers involving the breast, lung, prostate, and multiple myeloma. The majority of patients were treated for bony metastasis. However, some patients were treated with bisphosphonates for reasons other than their malignancy. Among the 6 patients who developed this complication, the distribution of primary malignancy was as follows: prostate cancer (n = 1), breast cancer (n = 1), multiple myeloma (n = 3), and renal cell carcinoma (n = 1). The mean treatment duration with bisphosphonate was 17 months (10–46 months) in patients diagnosed with osteonecrosis and 9 months (1–46 months) in patients without osteonecrosis. No significant relationships were observed between the incidence of osteonecrosis and age, sex, drug used, cumulative dose, or primary tumor.

The mandible was affected in 5 of 6 patients (83.3%) and maxilla in 1 of 6 patients (16.7%). Upon physical examination, all 6 patients were seen with exposed bone in the affected area (Figure 1). Osteonecrosis developed after dental treatment in 4 of 6 (66.7%) patients. In each patient, history and physical examination was used to confirm the diagnosis. Imaging included CT or nuclear medicine scans to assess the extent of bone loss or detect the presence of a sequestrum. A bone scan was obtained in 1 patient. This revealed markedly increased activity of the entire mandible demonstrating that the pathological process can be diffuse rather than confined to the focal area of exposed bone (Figure 2). Bisphosphonate therapy was discontinued in 5 patients upon diagnosis of osteonecrosis. The single patient who did not discontinue treatment had a small area of exposed mandibular bone, which was successfully covered by a rotational flap of adjacent mucosa. A second patient opted to resume bisphosphonate treatment after a 4-month suspension of therapy. These 2 patients were also managed with aggressive medical therapy including antibiotics, pen-

Table 1. Patient demographics.

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Pamidronate</th>
<th>Zoledronic acid</th>
<th>Pamidronate &amp; zoledronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>35–98</td>
<td>27–86</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>119</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>217</td>
<td>91</td>
</tr>
<tr>
<td>Primary diseases</td>
<td>Breast cancer</td>
<td>124</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
<td>44</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td>63</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Prostate cancer</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>68</td>
<td>35</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>Yes</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>332</td>
<td>169</td>
</tr>
</tbody>
</table>

Bisphosphonate-Associated Osteonecrosis
toxicodione, and vitamin E. Surgical management of the remaining 4 patients included debridement of exposed bone and mucosal rotation flaps, incision, and drainage of submental abscess in 1 patient, and external fixation for a pathologic fracture in the other. Histologic evaluation of bone debrided during surgery revealed necrotic bone with acute inflammation, consistent with osteomyelitis.

Among the 638 patients, 336 (52.7%) were treated with pamidronate alone, 169 (26.5%) with zoledronic acid alone, and 133 (20.8%) with both the agents. The incidence of osteonecrosis as a function of drug regimen was 4 of 336 (1.2%), 0 of 169 (0%), and 2 of 133 (1.5%) for each of these groups, respectively. These differences were not statistically significant.

The incidence of osteonecrosis was analyzed as a function of drug dosing parameters. This revealed that patients who developed osteonecrosis had a significantly greater mean number of infusions when compared with those who did not develop the complication (20.7 vs 10.7, \( p = .016 \)). Patients who developed osteonecrosis also underwent significantly greater cumulative hours of infusion (42.7 vs 17.7, \( p = .0036 \)). Cumulative drug dose and dosing interval were not significantly associated with the development of osteonecrosis. This is due to the variability of drug dose used in our study population. The individual drug dose varied with pamidronate, 30–90 mg—a majority of patients are treated with 90 mg—and zoledronic acid, 3–4 mg—a majority of patients are treated with 4 mg.

**FIGURE 1.** Mandibular osteonecrosis with exposed bone. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**FIGURE 2.** Nuclear medicine bone scan of mandibular osteonecrosis. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**DISCUSSION**

Bisphosphonate-associated osteonecrosis of the jaws may have significant morbidity ranging from minimal discomfort to significant loss of bone and function. Previous authors have reported incidences ranging from 1% to 10%.\(^5,8,9,12\) This study demonstrates a lower (0.94%) incidence of intravenous bisphosphonate-associated osteonecrosis. Bamias et al\(^5\) reported the incidence of this complication as 2.9% to 9.9% in their series of 252 patients treated with pamidronate or zoledronic acid with a higher rate observed in patients with multiple myeloma. Wang et al\(^12\) (\( n = 447 \)) noted an incidence of 2.5% to 3.8%, again with a higher incidence in patients with multiple myeloma. Hence, it is noteworthy that, in this series as well, multiple myeloma was the most prevalent underlying malignancy, accounting for 3 of the 6 cases.

Bisphosphonates are potent inhibitors of osteoclasts, retarding skeletal repair processes associated with trauma. It has been postulated that the constant use of the jaw bones resulting in minor trauma, and a continuum of bone remodeling is the cause of a preferential accumulation of the bisphosphonate which, in turn, leads to osteonecrosis.\(^10,13\) Other authors suggest that bisphosphonate-associated osteonecrosis of the jaws results from marked suppression of bone metabolism that results in accumulation of physiologic microdamage in the jaw bones, compromising biomechanical properties. Trauma and infection inherent to the location of the jaws within the oral cavity increases demand for osse-
ous repair, which exceeds the capacity of the hypodynamic bone. All 6 patients with bisphosphonate-associated osteonecrosis were seen with exposed bone. The complication occurred after dental treatment in two thirds of patients, and the mandible appears to be the most commonly involved site. These findings are also similar to the experiences of others as reported in smaller series. Invasive dental procedures causing trauma to the mucosa of the oral cavity may expose the underlying maxillary or mandibular bone and introduce oral flora. However, antecedent trauma may not be necessary for the development of osteonecrosis and underlying periodontal disease may also be a significant factor. Dental evaluation and treatment may decrease the incidence of bisphosphonate-associated osteonecrosis, but no studies to date have evaluated this theory. Previous authors recommend waiting for a month after invasive dental procedures to allow time for healing before commencing bisphosphonate therapy.

This study shows no statistical difference between drug used and the incidence of osteonecrosis. This is similar to findings of previously reported smaller series. Others, however, have observed a greater cumulative hazard in patients treated with zoledronic acid, compared with those receiving pamidronate or both agents. Although the number of osteonecrosis cases in this study is too small to determine a dose threshold, the increased incidence of osteonecrosis with a greater mean number of infusions was significant. Previous authors have also described a greater incidence of this complication with increased duration of therapy, suggesting that there is an underlying dose–response effect.

Management of osteonecrosis of the jaws remains a challenge. It should be noted that hyperbaric oxygen treatment has not been found to be effective in treatment of this disease. Infection of the necrotic bone can be a major issue requiring antibiotic therapy, nutritional support, and surgical drainage or debridement. Antibiotic therapy was used in all patients at this institution. Discontinuation of bisphosphonate therapy after diagnosis of osteonecrosis occurred in 5 of 6 patients at our institution. One patient resumed bisphosphonate therapy after resolution of osteonecrosis. Both of these patients had no indication of recurrent jaw complications at the time of this review. In both these patients, however, the degree of osteonecrosis was less severe than observed in the remaining 4 patients. Previous authors have stated that halting bisphosphonate therapy can neither reverse osteonecrosis nor help its symptoms. This finding is likely related to the long half-life of these drugs. Nonetheless, it appears prudent to consider suspension of therapy at least acutely. These observations suggest that management of bisphosphonate-associated osteonecrosis can be individualized according to disease severity and performance status of the patient.

CONCLUSION

Bisphosphonate-associated osteonecrosis is a recently recognized complication with an incidence of 0.94% in this study. This is the largest study examining all patients treated with intravenous bisphosphonate therapy at 1 institution and its relationship to osteonecrosis. A greater mean number of infusions and greater mean infusion time suggest a correlation between drug dose and osteonecrosis. However, these findings must be interpreted cautiously as the overall incidence of this complication was low. There is no statistical significance related to drug used, patient demographics, primary tumor, cumulative dose, or dosing interval. Dental comorbidity is a significant factor in development of osteonecrosis and should be addressed prior to initiating bisphosphonate therapy. Treatment of bisphosphonate-associated osteonecrosis should be individualized. This disease process has a wide range of potential effects, with an etiology that is not fully understood.

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REFERENCES