### A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients

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**Background:** Bone necrosis of the jaws is a newly recognized complication associated with the use of bisphosphonates. The true incidence of this complication is unknown and the pathophysiology is controversial. The purpose of this study was to determine the incidence of jaw necrosis among a homogeneous population of multiple myeloma patients receiving the bisphosphonate pamidronate, to investigate risk factors and comorbidities that increase the risk and to characterize the radiographic changes on conventional dental radiographs in terms of type and frequency.

**Materials and methods:** The study was a retrospective review of medical and dental charts and databases in the medical oncology and dental departments at Princess Margaret Hospital, a tertiary cancer centre in Toronto. Two patient sample sizes were used, \( n = 655 \) for assessment of the incidence and \( n = 120 \) for analysis of the risk factors and comorbidities.

**Results:** The incidence was estimated at 3.2% (95% confidence interval). The following risk factors were found to be statistically significant: longer duration of pamidronate therapy (\( P < 0.001 \)), dental extractions (\( P < 0.001 \)), cyclophosphamide therapy (\( P < 0.014 \)), prednisone therapy (\( P < 0.014 \)), erythropoietin therapy (\( P = 0.006 \)), low hemoglobin levels (\( P < 0.001 \)), renal dialysis (\( P < 0.016 \)) and advanced age (\( P < 0.001 \)). Radiographic changes produced by the necrotic bone were less evident than the clinically exposed bone.

**Key words:** bisphosphonate, bone exposure, bone necrosis, jaws, osteonecrosis, pamidronate

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**introduction**

Bisphosphonates play a key role in stabilizing metastatic osteolytic lesions of multiple myeloma, breast, prostate and other cancers, leading to a significant reduction of the associated complications such as pain and pathologic fractures [1, 2]. Although these drugs have been in clinical use for several years, a new complication termed osteonecrosis of the jaws was first reported in the literature in 2003 [3].

Osteonecrosis is defined as bone death due to obstruction of the blood supply [4]. As the exact disease mechanism for bone necrosis related to bisphosphonate therapy has not been established, the term ‘bone necrosis’ rather than osteonecrosis will be used in this paper. Two theories have been proposed as mechanisms for the drug-induced bone death. The first is a form of avascular necrosis similar to osteoradionecrosis [5, 6]. The second and more plausible is ironically the same mechanism that makes this family of drugs effective at controlling bone resorption: an alteration in the normal bone homeostasis process that repairs physiologic microdamage [2]. Nonhealing bone exposure of the jaws associated with bisphosphonates is most probably the result of a complex interplay of suppressed bone remodeling and hypovascularity compounded by local trauma (mechanical or infectious) [7].

Clinical presentation is characterized by mucosal dehiscence and bone exposure, with symptoms ranging from none to severe pain from secondary infections or trauma to the adjacent soft tissues [8, 9]. Radiographic findings vary from no evidence of bone changes to bone sclerosis, lytic areas and frank sequestration [1, 6]. Histologically, the findings are nonspecific and consist of acellular and necrotic osteons and a mixture of inflammatory cells [6]. *Actinomyces* organisms are frequently identified [9].

Bisphosphonate-related bone necrosis has been reported more frequently in patients receiving the more potent aminobisphosphonates, which are usually administered intravenously (IV), and occurs almost exclusively in the jaws [10]. The site-specificity is thought to be related to a higher
rate of jaw bone turnover due to the functional influence of teeth and the prevalence of dental diseases [3]. In addition, the jaws are the only bones that are covered by mucosa that may break down secondary to dental disease or invasive dental procedures exposing the bone to the oral flora, resulting in infection, which in turn may hinder the healing process [1, 5, 6].

A web-based survey funded by the International Myeloma Foundation was the first to estimate the incidence of bisphosphonate-associated jaw necrosis among patients receiving zoledronic acid and pamidronate at 10% and 4% respectively [11]. Several other studies explored the incidence of the complication and found it to range between 3% and 10% for multiple myeloma patients [10, 12].

Many risk factors and comorbidities have been proposed but few have been explored with supporting data. In a prospective study that followed 252 patients receiving bisphosphonates for at least 2 years, the type of bisphosphonate and the duration of use of the drug were the only two statistically significant risk factors [10]. Badros et al. investigated the complication among 90 multiple myeloma patients receiving pamidronate and zoledronic acid and found bone necrosis to be more prevalent with longer durations of therapy, in older patients and often after dental extractions [12]. There are no publications that study this complication using a homogeneous population of patients with the same disease and with the identical bisphosphonate drug regimen.

The aim of this study was to focus on a homogeneous population of multiple myeloma patients with the identical bisphosphonate regimen ( pamidronate IV 90 mg/month) and management protocol. Using this homogeneous population the study explored the frequency of this complication as well as many risk factors and comorbidities. The reported radiographic findings on conventional radiographs were also characterized in terms of type and frequency.

materials and methods
Ethical approval was obtained from the Cancer Registry and Data Access Committee, the University Health Network Research Ethics Board and the University of Toronto Research Ethics Board.

research design
A retrospective review of dental and medical charts and patient databases in both the dental and medical oncology departments of Princess Margaret Hospital (PMH), a tertiary cancer centre in Toronto, was completed. The dental database, which used FileMaker Pro6 (FileMaker, Santa Clara, CA), was instituted approximately 20 years ago to collect patients’ clinical data. There is a field entry for the examining dentist to record exposed necrotic bone of unknown cause. Incidents of necrotic bone were recorded in this database even though the relationship to bisphosphonate treatment was not yet proposed. The patient population consisted of multiple myeloma patients referred to the dental department for oral assessment prior to undergoing peripheral autologous stem cell transplants (ASCT). Two patient samples were used, a larger sample (n = 655) representing the total myeloma population seen at the dental clinic from September 2001 until the end of 2006 and a smaller sample (n = 120) representing multiple myeloma patients with sufficient available information for analysis of the risk factors and comorbidities. All 120 patients received a standard regimen of 90 mg pamidronate delivered monthly as 2-4 h IV injections. None of them received radiation therapy to the head and neck area.

data collection
The following data were collected for each patient of the population of 120: age, gender, date of first consultation at PMH, multiple myeloma subtype, presence or absence of skeletal lytic lesions by radiologic assessment at time of myeloma diagnosis, date of pamidronate therapy initiation, date of pamidronate discontinuation if applicable and chemotherapy regimen. Whether or not they received corticosteroids, immunosuppressants, erythropoietin or maintenance chemotherapy and whether or not they underwent ASCT was recorded. Data gathered also included other comorbidities, laboratory findings, status of the malignant condition at the last medical follow up and date and cause of death if applicable.

The complication of jaw bone necrosis was defined as nonhealing exposed bone of 8 weeks duration and/or radiographic evidence of sequestration in patients with a positive history of bisphosphonate therapy and a negative history of radiation therapy to the head and neck. For patients with the complication, the following additional data were collected: symptoms related to the exposed bone, number and location of lesions and the inciting dental event if applicable.

The presence of the following radiographic changes were recorded: sequestration, sclerosis, lysis, presence and progression of multiple myeloma lesions and presence of dental inflammatory diseases (periodontal, periapical and pericoron). This information was obtained from the patient radiographic report, which was based on panoramic and intra-oral radiographs and all dictated by the same oral and maxillofacial radiologist. The radiographic diagnostic criterion for bone necrosis was defined as the presence of sequestra.

statistical methods
Statistical analysis was performed using the SAS software Version 9.1 (SAS Institute, Cary, NC). Fifty variables were explored and were entered into a univariate logistic regression model. Variables were considered statistically significant if they retained a P value of $\leq 0.01$. The Kaplan–Meier method was used to estimate the median complication-free time.

results
The incidence of bone necrosis in a sample of 655 multiple myeloma patients seen at the PMH dental department was 21 cases or 3% (95% confidence interval [CI]).

The statistically significant risk factors and comorbidities that increase the risk of developing bone necrosis in a population of 120 multiple myeloma patients are duration of pamidronate exposure, dental extraction, cyclophosphamide, prednisone and erythropoietin treatment, low hemoglobin level, renal dialysis and age (Table 1). Kaplan–Meier analysis estimated the median complication-free time to be 7 years from the start of pamidronate therapy (Figure 1). The median follow-up time was approximately 2 years and the 2-year complication-free rate was calculated to be 89% (95% CI). The radiographic diagnosis of bone necrosis, based on the presence of sequestra, was made in 8 of the 24 patients with bone necrosis (Figure 2) but 42% of these 24 patients
Table 1. Statistically significant risk factors and comorbidities for developing pamidronate-related bone necrosis of the jaws

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pamidronate exposure (years)*</td>
<td>1.7</td>
<td>1.35–2.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dental extraction</td>
<td>5.3</td>
<td>2.05–13.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cyclophosphamide therapy</td>
<td>3.4</td>
<td>1.22–9.28</td>
<td>0.019</td>
</tr>
<tr>
<td>Prednisone therapy</td>
<td>6.5</td>
<td>1.44–29.47</td>
<td>0.014</td>
</tr>
<tr>
<td>Erythropoietin therapy</td>
<td>3.9</td>
<td>1.47–10.17</td>
<td>0.006</td>
</tr>
<tr>
<td>Low hemoglobin levelb</td>
<td>6.8</td>
<td>2.15–21.61</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal dialysis</td>
<td>3.2</td>
<td>1.23–8.25</td>
<td>0.006</td>
</tr>
<tr>
<td>Age (years)c</td>
<td>1.1</td>
<td>1.04–1.15</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Each additional year of pamidronate therapy increased the risk by 1.7 times.

bLow hemoglobin level was defined as less than the median, which was 121 g/L.

cEach additional year of life increased the risk by 1.1 times.

CI, confidence interval.

did not have any significant findings. The radiographic report recorded the following dental inflammatory diseases: periodontal disease in 79%, peri-apical disease in 21% and pericoronal disease in 4% of patients.

The majority of the lesions were located in the mandible (58%), with recent extraction sockets (38%) and the mylohyoid ridge (29%) being the most common locations. In addition, more than one lesion of exposed bone was detected in 17% of cases (Table 2). Interestingly only 39% of patients experienced pain, and macrotrauma, defined as any invasive dental procedure such as dental extraction, periodontal surgery or endodontic surgery, was the most common inciting event in 63% of cases.

Figure 1. Kaplan–Meier analysis.

Figure 2. Reported radiographic findings for 24 patients with bone necrosis. Note that several patients had more than one finding. WNL = within normal limits; MM = changes consistent with multiple myeloma.

discussion

The true incidence of bisphosphonate-associated bone necrosis is difficult to determine because of variables such as type, dosage, duration of the bisphosphonate treatment and patient variables including status of disease, age, other complicating diseases and other prescribed medications. In this study, an incidence of 3% was determined based on a homogeneous sample set of 655 multiple myeloma patients, all of whom received the same treatment of 90 mg of pamidronate monthly, thus reducing the influence of variables related to type of disease and the variety of bisphosphonate drug regimens. Although the data from the dental database program predate the recognition of bisphosphonate-related bone necrosis, it did successfully record bone necrosis, which was a field set up initially to capture bone necrosis of unknown causes. A possible error in this result would be failure of patients with the complication to attend the dental clinic.

Duration of pamidronate treatment was a significant risk factor and is supported by other studies involving a variety of bisphosphonates [10, 12, 13]. The long half-life of bisphosphonates in bone, estimated to be in the 10-year region, has been speculated to be the most plausible explanation [2, 12]. Dental extractions were a significant risk factor, as 64% of the patients with bone exposure had dental extractions. Invasive dental procedures including dental extractions, periodontal and endodontic surgery have been reported as major risk factors by Woo et al. [2]. Unfortunately, published studies are bereft of supporting data.

In this study, patients taking cyclophosphamide, an antineoplastic drug prescribed for relapsed multiple myeloma, had a marginally increased risk (P < 0.014) of developing the complication. In acute high doses, this drug has immunosuppressant properties and is administered prior to ASCT procedures. In chronic low doses, on the other hand, it has been shown to have immunostimulatory and antivasculogenic properties [14]. Prednisone, a corticosteroid, was found to be a significant risk factor,
which is in agreement with a published study by Durie et al. [13]. Corticosteroids are the second most common cause of avascular necrosis after trauma [15]. Their proposed mechanisms of action include hypercoagulability, fat emboli of small blood vessels and increased intrabony pressure due to hypertrophic lipid cells leading to mechanical obstruction of the blood flow [15]. It is possible that cyclophosphamide and prednisone may be acting synergistically with pamidronate to compromise the blood supply to bone, leading to bone death.

Migliorati et al. in an American Academy of Oral Medicine position paper concluded that jaw bone necrosis is most likely caused by a complex interplay of altered bone metabolism, increased demand for remodeling and repair, local infection and hypovascularity [7]. If indeed hypovascularity plays a role, then this could be exacerbated by the novel finding in this study that low hemoglobin levels increased the risk of developing bone necrosis. That erythropoietin treatment is also a significant risk factor may reflect the contribution of low hemoglobin as a risk factor. Alternatively, the thrombogenic potential of erythropoietin has been increasingly recognized in patients with malignancies, including myeloma [16]. Patients receiving this agent may therefore have an added risk of compromised blood flow to the affected area.

Renal failure is one of the conditions associated with nontraumatic osseous avascular necrosis (AVN) of the long bones [17]. The pathophysiology of AVN is not fully understood and is most likely multifactorial, with the final common pathway being interruption of the blood supply to the bones. If pamidronate treatment results in hypovascularity this may further exacerbate the vascular effects of renal disease. The finding of patient age as a significant risk factor is in agreement with Badros et al., who reported an increase in risk by 9% with each decade of life [12]. These authors interpreted this as a reflection of longer durations of bisphosphonate therapy although it is possible that changes in bone metabolism in the elderly may be an additional factor [12, 18].

Using evidence of bone sequestra in panoramic images as an indication of bone necrosis resulted in a positive radiographic report in 8 out of 24 patients. This finding is in contrast to reports by Ruggiero et al. and Marx et al., both of whom reported frequent positive radiographic findings but did not specify the type of radiographic images reviewed [1, 6]. This discrepancy is most likely due to a lack of consensus on the diagnostic radiographic criteria for bone necrosis. Widening of the periodontal ligament space, bone sclerosis and ‘moth-eaten’ lesions are signs of bone reaction but do not indicate bone necrosis [6, 19]. Badros et al. reviewed the panoramic radiographs of 22 cases and found most to be within normal limits of appearance [12]. Also, these authors commented that computed tomography (CT) was highly accurate in detecting cortical destruction, magnetic resonance imaging (MRI) was not useful, and positron emission tomography (PET) was nonspecific [12]. Studying conventional radiographs and CT, MRI and 99Tc(m)-MDP 3-phase bone scans of 11 patients, Chiandussi et al. concluded that panoramic radiographs were highly specific in detecting bone necrosis [20].

In conclusion, this study using a homogeneous population with the same malignancy and pamidronate regimen found the risk of developing bone necrosis increased with longer durations of pamidronate therapy, dental extractions and the use of cyclophosphamide, prednisone or erythropoietin therapy. The risk also increases with comorbidities, including low hemoglobin levels and renal dialysis. Advancing age is a strong determinant. Clarification of risk and comorbidity factors will help to prevent and treat bisphosphonate-related bone necrosis. Also this study supports theories of both bone remodeling inhibition and hypovascularity as playing a part in the pathophysiology of bisphosphonate-related bone necrosis.

**competing interest**

None of the authors have any financial and/or personal relationships with other people or organizations that could inappropriately influence or bias the work.
references