Osteomyelitis and necrosis of the jaw in patients treated with bisphosphonates: a comparative study focused on multiple myeloma

S. ELAD*, N. YAROM†,‡, W. HAMED*, S. AYALON*, R. YAHALOM§, E. REGEV*‡

*Department of Oral Medicine, The Hebrew University-Hadassah School of Dental Medicine, Jerusalem, Israel
†Department of Oral and Maxillofacial Surgery, ‘Sheba’ Medical Center, Tel-Hashomer, Israel
‡Department of Oral Pathology and Oral Medicine, The Maurice and Gabriela Goldschleger School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel
§Department of Oral and Maxillofacial Surgery, The Maurice and Gabriela Goldschleger School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel
*Department of Oral and Maxillofacial Surgery, The Hebrew University-Hadassah School of Dental Medicine, Jerusalem, Israel

Summary
It was reported that multiple myeloma (MM)-patients suffer from a higher incidence of osteomyelitis and necrosis of the jaws than patients treated with bisphosphonates for other reasons. The aim of this study is to report about 57 cases of bisphosphonate-related osteomyelitis and necrosis of the jaws (BON) and to investigate the differences between BON in MM and non-MM patients. Clinical and laboratory data of 57 cases were assessed. The features of BON and clinical-outcome were compared between the two groups. Treatment approach was assessed as a contributing-factor to treatment-outcome. Clinical presentation included exposed bone, pain, swelling and suppuration with little variation between the two groups. Past dento-alveolar surgery was common in both study-groups. Treatment outcome was poor (33% and 25% responded to treatment in MM group and non-MM group, respectively). Treatment modality did not affect the treatment outcome. The clinical presentation described in this case series should alert the physician to the possibility of BON. Although the literature shows a higher incidence of BON in MM patients compared to non-MM patients, our study suggests that the severity of the clinical presentation and the response to treatment are not worse in MM patients compared with non-MM patients. The predisposition of MM patients to BON should be further investigated.

Keywords
Myeloma, osteonecrosis, osteomyelitis, jaw, bisphosphonate, multiple myeloma

Introduction

Many multiple myeloma (MM) patients are treated with bisphosphonates, and this treatment prolongs survival in certain patients (McCloskey et al., 2001). Bisphosphonates also decrease skeletal complications, including vertebral fractures, nonvertebral fractures, bone pain, and hypercalcemia (Ruggiero et al., 2004; Hellstein & Marek, 2005; Marx et al., 2005; Migliorati et al., 2005).

Moreover, bisphosphonates are indicated for the treatment of hypocalcemia caused by malignancy (Coleman, 2000; Novartis, 2004, 2005), and for the prevention of skeletal complications including pathological fractures requiring surgical intervention in patients with bone metastasis of solid tumors (Hoffmann, 2003). Studies confirm the efficacy of bisphosphonate drugs in fracture prevention also in patients with osteoporosis and other skeletal diseases (Rogers, Watts & Russell, 1997: Reid, 2003).

Bisphosphonates are pyrophosphate analogues with variable potency with respect to distribution on the bone surface and osteoclast’s uptake (Rodan & Fleisch, 1996). Zoledronate and pamidronate are considered very potent (Hellstein & Marek, 2005).
Recently, osteomyelitis and necrosis of the jaws has been reported as a serious adverse event in bisphosphonate-treated patients (Marx et al., 2005; Migliorati et al., 2005; Pires et al., 2005). Clinically, these patients suffered from pain, swelling, exposed bone, and oral dysfunctions such as difficulty eating, swallowing and speaking.

Although the exact mechanism is unknown, there are evidences that bisphosphonates are a factor in the etiology of osteomyelitis and necrosis of the jaws. One must also consider that hematoncologic patients have additional risk factors for osteomyelitis and necrosis of the jaws, such as chemotherapy, radiotherapy (Neville et al., 2002) and chronic steroid use (Schwartz, 1982; Sung et al., 2002). Furthermore, recent studies suggested an increased incidence of bisphosphonate-related osteomyelitis and necrosis of the jaws (BON) in MM patients compared with other patient-groups (Bamias et al., 2005; Durie, Katz & Crowley, 2005). Therefore, research is essential to define the differences between BON in the general patient population and BON in MM patients.

This study will characterize a large group of MM patients treated with bisphosphonates and diagnosed with osteomyelitis and necrosis of the jaws. A group of non-MM patients with BON will be used to facilitate comparisons. A better understanding of the profile in each patient population may explain the difference in the incidence and will lead to the development of preventive and treatment protocols.

**Patients and methods**

This study was designed as a two-center, comparative-observational cohort study. The study was approved by the Ethic Review Board of both institutions. Inclusion criteria for the study were treatment with bisphosphonates – zolendronate (Zomera, Novartis, Linz, Austria), pamidronate (Aredia, Novartis, Linz, Austria), and alendronate (Fosalan, Merck sharp, Pavia, Italy) and a diagnosis of osteomyelitis and necrosis of the jaws.

Data retrieved from patient files included: (i) demographic parameters (age, gender); (ii) clinical parameters: symptoms, signs, site, size (lesion size was described in terms of the number of teeth or equivalent alveolar ridge span of lesion); (iii) history of dentoalveolar procedures; (iv) histopathological findings; (v) microbiological findings (cultures and staining); (vi) underlying disease; (vii) treatment for underlying disease (chemotherapy, radiotherapy, steroid therapy); (viii) management of the lesion (type, extent and number of interventions).

Treatment outcome was classified: (i) a positive outcome defined as ‘healing of the lesion’ (partial or complete) and ‘healing with relapse at another site’; (ii) a negative outcome defined as lesions, which demonstrated ‘nonhealing’ or ‘healing with relapse at the same site’. Only patients with at least 2 months of follow-up were included in the treatment outcome evaluation. Statistical correlations between an underlying diagnosis of MM and the clinical outcome were analyzed using Fisher’s exact test. Correlations between treatment parameters (surgical, nonsurgical) and the clinical outcome were calculated in the same way.

**Results**

**Patient characteristics**

Fifty-seven patients were included in this study. Twenty-two patients diagnosed with MM were compared with 35 patients suffering from other diseases (Table 1).

Other underling diseases of the MM patient-group included: hypertension 41% (nine of 22 cases) and type 2 diabetes mellitus 22% (five of 22 cases). Less common background diseases were asthma, renal failure, and hyperlipidemia. At the time of diagnosis of BON, all patients were treated with additional medications, the most common were metformin hydrochloride (Glucophage, Teva pharmaceutical industries, Ramat Hasharon, Israel), atenolol (Normiten, Teva pharmaceutical industries, Ramat Hasharon, Israel), and atorvastatin (Lipitor, Godecke, Gubtt, Germany).

**Bisphosphonate treatment**

Three types of bisphosphonates were used: zolendronate, pamidronate, and alendronate (Table 1). Sixty percent of the patients (34 of 57 patients) were treated with pamidronate, administered intravenously with an average dose of 82 mg/month. Thirty-two percent of the patients (18 of 57 cases) were treated with 4 mg of IV zolendronate per month. Alendronate was used orally in 8% of patients (five of 57 cases) with an average weekly dose of 70 mg.

**BON clinical presentation**

Among the all patients, exposed bone, pain, swelling, and suppurating fistulas were the predominant clinical features (Table 2, Figure 1). Mandibular involvement was more prevalent than maxillary in both group (Table 2). Lesions developed after a local dentoalveolar surgical procedure (extraction, biopsy or dental implant placement) in both groups.

The clinical presentation in MM patients was similar to the findings in the non-MM patients with respect to the time between local surgery and diagnosis, lesion size and...
the affected jaw (Table 2). Six patients had BON in multiple sites, two of which were in MM patients.

**Laboratory findings**

Microbiological cultures (total of 32) and tissue specimens (total of 31) were taken from the lesions in order to identify local infection or to exclude local malignancy (Table 3). Histological presentation was typical to osteomyelitis in all patients demonstrating inflammatory infiltrate and necrotic bone. *Actinomyces* was identified and *Streptococcus viridans* was isolated (Table 3). In the MM patients, *Actinomyces* was identified in eight of 17 cases (47%) and *Streptococcus viridans* was isolated in five of 11 cases (45%). In the non-MM patients *Actinomyces* was observed in nine tissue specimens and *Streptococcus viridans* was evident in nine cultures.

**Evaluation of treatment modalities**

Surgical and nonsurgical approaches were used to treat the patients. Surgical treatments included superficial debridment, curettage, and extensive surgery. In 56% of cases (32 of 57), treatment consisted of limited surgical procedures. In two cases extensive surgical procedures were performed (hemimaxillectomy and hemimandibulectomy). Eighteen cases (30%) were treated nonsurgically with one or more of the following: antibiotics, topical

---

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Main diagnosis</th>
<th>Multiple Myeloma</th>
<th>Solid tumors*</th>
<th>Osteoporosis</th>
<th>Other†</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>22</td>
<td>25</td>
<td>6</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>Age (years; average ± SD)</td>
<td>62.86 ± 9.58</td>
<td>61 ± 12.23</td>
<td>64.66 ± 9.13</td>
<td>68.2 ± 10.3</td>
<td>62.74 ± 10.8</td>
</tr>
<tr>
<td>Gender (M : F)</td>
<td>12 : 10</td>
<td>3 : 22</td>
<td>0 : 6</td>
<td>1 : 3</td>
<td>16 : 41</td>
</tr>
</tbody>
</table>

Bisphosphonate type (no. patients)
- Pamidronate 17
- Zoledronic acid 4
- Alendronic acid 1

Previous chemotherapy (no. patients)
- S/P BMT (no. patients) 8

**Table 2. Clinical presentation**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>MM (n = 22)</th>
<th>Other (n = 35)</th>
<th>Total (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed bone (%)</td>
<td>18 (82)</td>
<td>27 (77)</td>
<td>45 (79)</td>
</tr>
<tr>
<td>Pain (%)</td>
<td>16 (73)</td>
<td>26 (74)</td>
<td>42 (75)</td>
</tr>
<tr>
<td>Swelling (%)</td>
<td>9 (41)</td>
<td>16 (64)</td>
<td>25 (44)</td>
</tr>
<tr>
<td>Fistula (%)</td>
<td>9 (41)</td>
<td>13 (37)</td>
<td>22 (39)</td>
</tr>
<tr>
<td>Postsurgical (%)</td>
<td>19 (86)</td>
<td>26 (74)</td>
<td>45 (79)</td>
</tr>
<tr>
<td>Spontaneous (%)</td>
<td>3 (14)</td>
<td>7 (20)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Time to diagnosis postsurgery (%)</td>
<td>10.29 ± 10.8</td>
<td>6.95 ± 5.82</td>
<td>7.95 ± 8.08</td>
</tr>
<tr>
<td>Lesion size (tooth span; average ± SD)</td>
<td>1.45 ± 1.1</td>
<td>1.4 ± 0.702</td>
<td>1.41 ± 1.1</td>
</tr>
<tr>
<td>Maxilla : Mandible</td>
<td>9 : 13</td>
<td>14 : 21</td>
<td>23 : 34</td>
</tr>
</tbody>
</table>

*Missing data for two patients in the non-MM group.
MM, multiple myeloma; SD, standard deviation.
agents (chlorhexidine, saline), palliative treatments (local anesthetics, analgesics, and narcotics), and hyperbaric-oxygen (HBO).

Thirty-nine patients were included in the treatment outcome analysis. The mean follow-up period of this group was 4.7 ± 2.3 months. A positive outcome was observed in 28% of all patients (11 of the 39), and a negative outcome was apparent in 72% of all patients (28 of the 39; Table 4). In the surgically treated patients the negative outcome rate was even higher (78%; \( P = 0.26 \)). In the MM group, treatment was slightly more successful (six of 18 patients) compared with the non-MM patients (five of 20 patients, \( P = 0.72 \)).

### Discussion

In the last 2 years, there have been increasing number of reports of osteomyelitis and necrosis of the jaws in bisphosphonate-treated patients (Marx, 2003; Tarassoff & Csermak, 2003; Lugassy et al., 2004; Ruggiero et al., 2004; Marx et al., 2005; Migliorati et al., 2005; Olson, Hellie & Pienta, 2005; Pires et al., 2005). Two recent studies stated that MM patients suffer from BON more frequently than other patients (Bamias et al., 2005; Durie, Katz & Crowley, 2005). Thus, it is important to outline the extent of bisphosphonate related morbidity in this group of patients and to delineate the differences in BON between MM and non-MM patients.

The most common clinical manifestations in both groups in our study were exposed bone and localized jaw pain. This finding is consistent with the literature (Marx, 2003; Marx et al., 2005; Pires et al., 2005). Pain incidence was reported to range between 69% and 100% (Ruggiero et al., 2004; Marx et al., 2005; Migliorati et al., 2005; Pires et al., 2005), and one can assume that secondary infection contributes to pain (Marx, 2003; Lugassy et al., 2004; Marx et al., 2005; Migliorati et al., 2005; Pires et al., 2005). Our findings demonstrated a high incidence of co-infection in specimens and cultures taken from the lesions, which is consistent with the literature. The dominant microorganisms observed were *Actinomyces* and *Streptococcus viridans*, which in certain conditions may be part of the normal oral flora.

#### Table 3. Microbial findings

<table>
<thead>
<tr>
<th></th>
<th>No. patients with a positive microbial test (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Previous surgical procedure</td>
</tr>
<tr>
<td><em>Actinomyces</em></td>
<td></td>
</tr>
<tr>
<td>((n = 31))</td>
<td>8 (26)</td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
<td>5 (16)</td>
</tr>
</tbody>
</table>

#### Table 4. Treatments and outcomes

<table>
<thead>
<tr>
<th>Treatment type*</th>
<th>Lesion’s size†</th>
<th>Positive outcome</th>
<th>Negative outcome</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical ((n = 27))</td>
<td>1.7 ± 1.05</td>
<td>6 (22)</td>
<td>21 (78)</td>
<td>0.26</td>
</tr>
<tr>
<td>Nonsurgical ((n = 12))</td>
<td>1.65 ± 1.11</td>
<td>5 (42)</td>
<td>7 (58)</td>
<td></td>
</tr>
<tr>
<td>MM ((n = 18))</td>
<td>1.45 ± 1.1</td>
<td>6 (33.3)</td>
<td>12 (66.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Non-MM ((n = 20))</td>
<td>1.4 ± 0.702</td>
<td>5 (25)</td>
<td>15 (75)</td>
<td></td>
</tr>
</tbody>
</table>

*Fisher’s exact test.
†Tooth span (average ± SD).

no., number; MM, multiple myeloma.
The optimal treatment for BON is unknown. In this comparative study, surgical treatment failed more often than nonsurgical treatment. Although this difference was not statistically significant, this trend can be seen in previous descriptive studies (Lugassy et al., 2004; Marx et al., 2005; Migliorati et al., 2005). Actually, according to Marx et al. (2005), surgery often resulted in further deterioration. Therefore, systemic culture-based antibiotic treatment, and basic oral care should serve as the first line of treatment. Surgery may be indicated for more extensive lesions.

The comparison between MM and the non-MM patient groups showed that the MM group had a higher positive response rate to treatment; however, the difference was not statistically significant. We suspect that a more homogenous MM-group with respect to bisphosphonate type would clarify the clinical significance of our results. It is important to note that most of the MM patients received pamidronate, while, in the non-MM group, a smaller portion of the patients received this bisphosphonate. Pamidronate is known to be less potent than zolendronate and this may effect the treatment outcome (Hellstein & Marek, 2005).

At present there are many unanswered questions about the pathogenesis of BON (Reszka & Rodan, 2003; Hellstein & Marek, 2005). Bisphosphonates act on multiple pathways, of which osteoclast inhibition is the most dominant. They inhibit osteoclasts (Rodan & Fleisch, 1996; Hellstein & Marek, 2005; Marx et al., 2005; Migliorati et al., 2005; Pires et al., 2005), thereby disturbing the balance of bone remodeling and facilitating the creation of dense compact bone (Rodan & Fleisch, 1996; Marx et al., 2005; Migliorati et al., 2005). Osteoclasts are downregulated through apoptosis, reduced induction, activation of osteoclast inhibitory factors, inhibition of osteoclast development, and inhibition of osteoclast activating factors such as receptor activator of NF-κB ligand (RANKL) (McCloskey et al., 2001; Reszka & Rodan, 2003; Ruggiero et al., 2004; Hellstein & Marek, 2005; Marx et al., 2005). Other possible mechanisms include effects on stromal cell pathways. Bisphosphonates also inhibit the activation of matrix metalloproteinase (MMP-1 and MMP-2) preventing collagen degradation, also resulting in the production of dense, compact bone (Teronen et al., 1999; McCloskey et al., 2001). Fournier et al. (2002) have shown that as well as inhibiting angiogenesis (Curi & Dib, 1997; Ruggiero et al., 2004; Bukowski, Dascher & Das, 2005; Marx et al., 2005), bisphosphonates decrease capillary tube formation and inhibit endothelial factor sprouting and endothelial cell proliferation. All of the effects mentioned above may explain the avascular exposed bone seen in the jaws after bisphosphonate use. Interestingly, pamidronate increases the susceptibility of hydroxyapatite to Staphylococcus aureus, which may facilitate recruit local inflammatory processes (Ganguli et al., 2005).

Of note is the contribution of additional suspected risk factors such as the disease state and current anticancer treatment. Many of the patients in this study were referred to our clinic at an advanced stage of the pathological condition. As some other patients in this study were asymptomatic, BON was diagnosed incidentally. Therefore, onset of BON preceded the diagnosis in many of the cases. All surgical procedures were preformed while no anticancer treatment was administered. Thus, the effect of disease state and anticancer treatment on the development of BON, or its response to treatment, cannot be assessed from this group of patients.

In summary, this is the first comparative study focusing on MM patients diagnosed with BON. We found that although the incidence of BON is higher in MM patients compared to non-MM patients, the severity of the clinical presentation and the response to treatment are not worse in MM patients compared with non-MM patients. More research is needed to elucidate the molecular mechanisms of BON in order to understand the predisposition of MM patients to this complication, and to find the best treatment or prevention.

**Acknowledgements**

The authors would like to thank Dr SDM Robinson for her editorial assistance and Dr M Baras for the statistical analysis.

**References**


