Abstract. Background: Intravenous bisphosphonates are the current standard of care for the treatment of hypercalcemia of malignancy and for the prevention of skeletal complications associated with bone metastases. Recently, retrospective case studies have reported an association between long-term bisphosphonate therapy and osteonecrosis of the jaws. Patients and Methods: The data for twelve patients, referred to either an oral and maxillofacial surgeon or to an oral medicine specialist for the management of clinically apparent chronic oral osteonecrosis of unknown etiology, were reviewed. All had received cancer-related therapy simultaneously with bisphosphonate management. Results: The typical presenting symptoms were pain and exposed bone at the site of a previous tooth extraction. In most patients, the lesions initially occurred after dental extraction or other odontostomatological procedures, while five had a spontaneous event. Biopsy of the involved area showed the presence of necrotic lacunae, with infiltration of lymphocytes and histiocytes. In nine cases, there was histological or cytological diagnosis of suspicious osteomyelitis. No correlation was observed between the intraoral lesions and myelosuppression secondary to antineoplastic therapy. Conclusion: Based on the patients' respective histories, clinical presentations and responses to surgical and antibiotic treatments, it appears that the pathogenesis of this osteonecrotic process is most consistent with localized vascular insufficiency. In our opinion, the mechanism by which bisphosphonates compromise bone vascularity may be related to their effect on the osteoclasts. The potent bisphosphonate-mediated inhibition of osteoclast function serves to decrease bone resorption and inhibit normal bone turnover remodeling, resulting in microdamage accumulation and a reduction in some mechanical properties of the bone.

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and are effective in the treatment of malignant bone disease (1). Intravenous bisphosphonates are the current standard of care for the treatment of hypercalcemia of malignancy and for the prevention of skeletal complications associated with bone metastases. Currently, zoledronic acid (4 mg via a 15-min infusion) and pamidronate (90 mg via a 2-h infusion) are the only agents recommended by the American Society of Clinical Oncology (ASCO) for the treatment of bone lesions from breast cancer and multiple myeloma (2). Furthermore, zoledronic acid is approved by both the U.S. Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for the prevention of skeletal complications in patients with multiple myeloma, or bone metastases secondary to a variety of solid tumors, including breast, prostate and lung cancer (3).

The bisphosphonates used to treat malignant bone disease are administered either orally or via an intravenous (i.v.) infusion. Although daily oral bisphosphonate therapy can be administered at home and may seem more convenient for the patient than i.v. administration, this oral therapy appears to be less effective and may ultimately not be any more convenient than monthly infusions (4-6).

In general, the i.v. administration of bisphosphonates is well-tolerated with a predictable and manageable side-effect profile that may include acute-phase responses, fluctuations in serum ion levels (calcium, magnesium and phosphorus) and occasional elevations in serum creatinine (7, 8). However, i.v. bisphosphonates are associated with a low incidence of serious adverse events. In addition, there are no known interactions

Correspondence to: Enzo Veltri, MD, Department of Medical Oncology, "A. Fiorini" Hospital, 04019 Terracina (LT), Italy. Tel: +39(0)773-708793, Fax: +39(0)773-708792, e-mail: aslter.oncoterracina@libero.it

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between the bisphosphonates and anticancer agents. Self-limiting, transient, acute-phase reactions, resulting in mild to moderate influenza-like symptoms, have been reported in approximately one-third of patients, primarily after the first infusion (7). In the comparative phase III trial of 4 mg zoledronic acid versus 90 mg pamidronate in patients with breast cancer or multiple myeloma, the most common adverse events in both treatment groups were mild to moderate bone pain, nausea, fatigue and fever, these events occurring with similar frequencies in both treatment groups (9, 10).

Recently, retrospective case studies have reported an association between long-term bisphosphonate therapy and osteonecrosis of the jaws (11-13). The incidence of osteonecrosis was very rare, occurring in <1 in 10,000 patients receiving i.v. bisphosphonate therapy since 2001. Historically, the risk of developing osteonecrosis (at any site) is four times higher in cancer patients than in the normal population and has multiple risk factors, including previous/concomitant chemotherapy, steroid therapy, or radiation therapy, as well as trauma, infection and a history of dental procedures (14-15).

Patients and Methods

The data for twelve patients, referred to either an oral and maxillofacial surgeon or to an oral medicine specialist for the management of

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Gender</th>
<th>Tumor</th>
<th>Chemotherapeutic agents</th>
<th>Biphosphonates used</th>
<th>Time used (mo.)*</th>
<th>Oral manifestation</th>
<th>Therapy</th>
<th>Histopathology</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>Female</td>
<td>Breast</td>
<td>cyclophosphamide, methotrexate and 5-fluorouracil (CMF), Tamoxifen, letrozole</td>
<td>zoledronic acid</td>
<td>26</td>
<td>Infection, osteonecrosis</td>
<td>Antibiotics</td>
<td>Osteonecrosis</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>Female</td>
<td>Breast</td>
<td>Tamoxifen, letrozole, anastrozole, exemestane</td>
<td>zoledronic acid</td>
<td>18</td>
<td>Infection, osteonecrosis</td>
<td>Antibiotics</td>
<td>NA</td>
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<tr>
<td>3</td>
<td>72</td>
<td>Female</td>
<td>Lung</td>
<td>Gemcitabine, cisplatin, paclitaxel, docetaxel, gefitinib</td>
<td>zoledronic acid</td>
<td>19</td>
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<td>Sequestrectomy, antibiotics</td>
<td>Osteonecrosis</td>
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<tr>
<td>4</td>
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<td>Kidney</td>
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<td>28</td>
<td>Infection, osteonecrosis</td>
<td>Antibiotics</td>
<td>Osteonecrosis</td>
</tr>
<tr>
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<td>78</td>
<td>Female</td>
<td>Breast</td>
<td>CMF, tamoxifen, letrozole</td>
<td>zoledronic acid</td>
<td>16</td>
<td>Infection, osteonecrosis</td>
<td>Sequestrectomy, Antibiotics</td>
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<tr>
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<td>Male</td>
<td>Lung</td>
<td>Gemcitabine, carboplatin</td>
<td>pamidronate, zoledronic acid</td>
<td>16</td>
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<td>Antibiotics</td>
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</tr>
<tr>
<td>7</td>
<td>58</td>
<td>Female</td>
<td>Breast</td>
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<td>zoledronic acid</td>
<td>22</td>
<td>Infection, osteonecrosis</td>
<td>Resection, antibiotics</td>
<td>Osteonecrosis</td>
</tr>
<tr>
<td>8</td>
<td>78</td>
<td>Female</td>
<td>Breast</td>
<td>Tamoxifen, cyclophosphamide, letrozole</td>
<td>zoledronic acid</td>
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<td>Resection, antibiotics</td>
<td>Osteonecrosis</td>
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<tr>
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<td>64</td>
<td>Female</td>
<td>Breast</td>
<td>Tamoxifen, cyclophosphamide, letrozole</td>
<td>zoledronic acid</td>
<td>18</td>
<td>Infection, osteonecrosis</td>
<td>Resection, antibiotics</td>
<td>Osteonecrosis</td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>Male</td>
<td>Multiple myeloma</td>
<td>ND</td>
<td>zoledronic acid</td>
<td>NA</td>
<td>Infection, osteonecrosis</td>
<td>Resection, antibiotics</td>
<td>Osteonecrosis</td>
</tr>
<tr>
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<td>Female</td>
<td>Multiple myeloma</td>
<td>ND</td>
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<td>NA</td>
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<td>Resection, antibiotics</td>
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<td>Breast</td>
<td>Tamoxifen, cyclophosphamide, letrozole, methotrexate</td>
<td>zoledronic acid</td>
<td>16</td>
<td>Infection, osteonecrosis</td>
<td>Resection, antibiotics</td>
<td>Osteonecrosis</td>
</tr>
</tbody>
</table>

*Length of time biphosphonates were received reflects the time from start of therapy to the first clinical detection of osteonecrosis. NA: not available.
clinically-apparent chronic oral osteonecrosis of unknown etiology, were reviewed. All the patients had received cancer-related therapy simultaneously with bisphosphonate management.

Patient information, primary malignancy, oncological treatment and the use of bisphosphonates are reported in Table I. There were nine females and three males with a mean age of 69 years (range, 58-78). The malignancies included breast carcinoma (n=7), multiple myeloma (n=2), prostate carcinoma (n=1), non-small cell lung cancer carcinoma (n=2) and kidney carcinoma (n=1). The typical presenting symptoms were pain and exposed bone at the site of a previous tooth extraction. Because of similarities among the patients, a summary description of the common history, clinical, radiographical and histopathological findings and patient management is presented.

Results

In most patients, the lesions initially occurred after dental extraction or other odontostomatological procedures, while five patients had a spontaneous event. The patients started to complain of jaw pain, difficulty in masticating and in brushing their teeth. The clinical appearance simulated dental abscesses or osteomyelitis (Figure 1, 2a, 2b). Biopsy of the involved area showed the presence of necrotic lacunae, with infiltration of lymphocytes and histiocytes. In nine cases, a histological or cytological diagnosis of suspicious osteomyelitis was made. There was no observed correlation between the intraoral lesions and myelosuppression secondary to antineoplastic therapy. At the time of consultation, other potential etiological risk factors for osteonecrosis were investigated, but none could be identified. These factors included dental and family history, social lifestyle, tobacco or alcohol use, or radiotherapy to the head and neck. The exposed bone surface, in the early stage of the process, was smooth. However, with progression of necrosis, some patients developed an irregular rough bony surface, that was probably due to fracture of the necrotic bone during mastication. Pain appears to have resulted from either secondary infection of the surrounding soft tissue areas or from trauma to opposing soft tissue areas (e.g., lateral tongue). The most common site of the bone necrosis was the posterior/lingual mandible, in the area of the mylohyoid ridge.

Bone necrosis was typically progressive and, with the subsequent involvement of the adjacent teeth, often led to compromised oral hygiene of the dentition contiguous to the lesion. The past dental history of many of the patients revealed recent tooth extraction, with subsequent osteonecrosis of the alveolar socket, and delayed healing or non-healing of the extraction site. Injury to contiguous neural tissue also may have occurred.

Discussion

The bony lesions occurring in twelve patients with cancer managed at several institutions are described here. The lesions represent an emerging oral complication of
bisphosphonate therapy, especially in patients with cancer and skeletal metastasis.

Based on these patients' respective histories, clinical presentations and responses to surgical and antibiotic treatments, it appears that the pathogenesis of this osteonecrotic process was most consistent with localized vascular insufficiency. The lesion's clinical similarity to osteoradionecrosis, with compromised bone that sequestrates either spontaneously or after a minor procedure, followed by secondary infection, is striking. In our opinion, the mechanism by which bisphosphonates could compromise bone vascularity may be related to their effect on the osteoclasts. The potent bisphosphonate-mediated inhibition of osteoclast function serves to decrease bone resorption and inhibit normal bone turnover remodeling, resulting in microdamage accumulation and a reduction in some mechanical properties of the bone (16). However, bone resorption and remodeling play an essential role in maintaining normal bone homeostasis. As osteoclastosis occurs, a host of cytokines and growth factors are released into the surrounding matrix, which are essential for modulating new bone development. The inhibition of new bone formation can affect the quality of bone during growth and fracture healing. Metaphyseal sclerotic banding is a documented effect of periodic bisphosphonate treatment in growing children (17, 18). Whyte et al. (19) reported a case of osteopetrosis that developed in a child receiving high-dose pamidronate over a 2-year period, where it was noted that the endochondral bone was not remodeled and became encased within trabecular bone. In fracture repair, the bisphosphonate-mediated inhibition of bone remodeling results in a more profound and larger callus, with uncompromised mechanical integrity (20-22). Bisphosphonates also have shown effects unrelated to osteoclast inhibition.

Pamidronate has been associated with an acute-phase reaction, characterized by fever and transient changes in various cytokine levels such as interleukin-6, tumor necrosis factor-α, C-reactive protein and elastase (23). More importantly, pamidronate was reported to significantly depress the bone blood flow in rats (24, 25). The mechanism of this effect may be attributable to a complex interaction of pamidronate with growth hormone and insulin-like growth factor I, both of which are thought to play a role in the regulation of blood circulation in the bones. In a recent study, the bisphosphonates were shown to inhibit endothelial cell function in vitro and in vivo (26). The cells treated with bisphosphonates showed decreased proliferation, an increased rate of apoptosis and a decrease in capillary- tube formation (26). In the same study, there was a marked reduction in the number of blood vessels in pagetic bone marrow after bisphosphonate treatment compared to the pretreatment biopsy results. Bisphosphonates have also shown potent anti-angiogenic properties due to their ability to significantly decrease the circulating levels of vascular endothelial growth factor (a potent angiogenic factor) in breast cancer patients with bone metastases (27). Wood et al. (28) showed the anti-angiogenic properties of the bisphosphonates on several levels: a) potent inhibition of vessel sprouting in a chick embryo model and b) potent inhibition of angiogenesis induced by subcutaneous implants impregnated with basic fibroblast growth factor in a murine model. These previously unrecognized anti-angiogenic properties have generated interest in using bisphosphonates as potential antitumor agents (29). Furthermore, these bisphosphonate properties could explain the apparent ischemic changes noted in our patients' mandibles and maxillae. These complications were not recognized during the trial stages of these drugs, suggesting that the ischemic effects may be cumulative in nature. The apparent selective involvement of the maxilla and mandible in these patients may be a reflection of the unique environment of the oral cavity. Typically, healing of an open bony wound (e.g., extraction socket) in the presence of oral microflora occurs quickly and without infection. However, when the vascular supply of the mandible or maxilla is compromised by either radiation therapy or some other agent(s), then minor injury or disease in these sites is much more likely to develop into a non-healing wound. That, in turn, can progress to widespread necrosis and osteomyelitis. Unlike patients with osteoradionecrosis, necrosis of the maxilla was common in bisphosphonate patients despite the inherently rich vascular supply of the maxilla. If, however, a blood-borne agent was responsible for the bone necrosis, the maxilla would certainly be at risk of developing disease, given its vascularity and its potential for increased exposure. The chemotherapeutic agents and steroid preparations taken by these patients can also affect wound healing, and must be considered to be a possible etiological factor. Another consideration is that these chemotherapy agents act synergistically with bisphosphonates to promote bone necrosis.

The management of patients with bisphosphonate-related osteonecrosis remains extremely difficult. In addition to the preventive measures mentioned above, surgical intervention undoubtedly plays a role in bis-phossy jaw therapy. We may need to develop a staging protocol regarding when surgical intervention should be considered. As described by Ruggiero et al. (13), extensive involvement may necessitate large areas of debridement to include segmental mandibulectomy and partial maxillectomy, although the best method of treating bisphossy jaw is still being explored. Sequential removal of sequestra as necessary is the current conservative approach but, if large volume debridement becomes necessary, the goal should be to remove as little bone as possible. Marx (11) reported the futility of trying to cover the exposed areas with tissue flaps. When removing bone, the clinician must realize that there is no periphery of "normal" bone because the entire skeleton is being treated with the bisphosphonate. The maintenance of as much periosteum as possible should also
help to minimize the amount of bone exposed to the oral microbiological flora. Multiple treatment protocols may be necessary in the search for the best method to treat bis-phossy jaw; in treatment development, multiple factors should be taken into consideration and recorded.

Patient attributes, clinical findings, clinical and medical co-factors, patient compliance issues, follow-up intervals and the therapeutic modalities used should all be annotated in each case. Much more research is necessary to identify which population groups or oral factors are the best risk predictors of bis-phossy jaw.

There is no doubt that bisphosphonate therapy will continue to show substantial clinical benefits and be used more extensively. It can also be predicted that the percentage of people affected with bis-phossy jaw may ultimately prove to be relatively low, through the overall number affected will be clinically significant. The morbidity of affected patients is proving to be very significant. The ideal dosage and delivery route of bisphosphonate for each patient category need to be determined. In addition, it is imperative that predictive and preventive dental metrical characteristics metrics, along with treatment categories and protocols, be established.

References


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