Bisphosphonates and jaw osteonecrosis in patients with advanced breast cancer

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Background: In recent years, several cases of mandibular necrosis associated with long-term use of bisphosphonates have been reported. The estimated incidence varies from 1% to 4.6%.

Patients and methods: We conducted an observational study with the aim of determining the incidence of jaw osteonecrosis in advanced breast cancer patients with bone metastases under bisphosphonate treatment and to identify subjects at higher risk of developing this complication evaluating preclinical signs. We considered two groups of patients. All the patients complaining of odontostomatological symptoms underwent maxillary CT scan and maxillo-surgeon clinical examination. Asymptomatic patients were asked to perform a standard orthopantomography (OPT).

Results: From February 2005 to October 2005, we observed five patients with jaw bone necrosis (6%). Diagnosis was radiological and clinical. In two patients a confirmatory biopsy was performed. In the same time interval, OPTs were collected from 76 asymptomatic patients. Three OPTs revealed radiological features of suspicious mandibular necrosis. Maxillary CT scan confirmed the presence of an osteolytic area with signs of periosteal reaction. All the three patients were referred to maxillo-surgeon and two out of three patients underwent mandibular biopsy, but histopathological results were not conclusive.

Conclusions: In our experience, the incidence of jaw bone necrosis in breast cancer patients seems to be higher than in other reports (6%). Radiological features of suspicious jaw necrosis were observed in three asymptomatic patients. We do not know how these findings should be considered. Anyway, standard OPT is a simple procedure, and may allow identification of periodontal conditions that in some way can predispose to the development of this uncommon event.

Key words: breast cancer, osteonecrosis, bisphosphonates

Introduction

Bisphosphonates are currently used to prevent bone complications and to treat malignant hypercalcemia in patients with multiple myeloma, and in case of bone metastases due to breast and prostate cancer [1–4]. In last years, several cases of mandibular necrosis associated with long-term use of bisphosphonates have been reported [5–7].

The real incidence is unknown due to the fact that most of the cases are spontaneous reports, or results of retrospective analyses; the estimated incidence varies from 1 to 4–6% [8–10]. Clinical presentation is often preceded by odontostomatological procedures. This relatively uncommon condition can severely affect quality of life, even becoming the major concern of cancer patients. Patients complain of local pain, difficulties in performing oral hygiene and in eating, leading eventually to severe weight loss. They usually present with exposed avascular bone in the mandible, mainly localized in the lower jaw. This pathological feature, identified as ‘jaw avascular bone necrosis’, appears as a growing, painful, unilateral swelling of the mandible in patients receiving bisphosphonates [6, 11, 12].

Clinical and histopathological differential diagnosis with mandibular metastases or osteomyelitis is often required. Ethiopathogenesis is unclear; no definitive cure has yet been established.

Prevention and early identification of patients at risk should be of prime concern [13, 14].

We conducted an observational study with the aim of defining the incidence of jaw osteonecrosis in our Institution and to identify subjects at high risk of developing this complication evaluating preclinical signs, in particular radiological modifications.

Like osteoradionecrosis the radiographic features of mandibular necrosis associated with long-term use of bisphosphonates have many similarities to that of chronic osteomyelitis [6, 15]. The radiological appearance of the internal
structure is complex and results in a combination of bone sclerosis and destruction around the teeth and alveolar crest [15]. In our experience based on evaluation of radiographic and CT exams in most of the lesions the more radio-opaque or sclerotic pattern is prevalent, obscuring the normal bone trabeculae. Computed tomography (CT) helps in differential diagnosis from jaw metastases. CT is superior to orthopantomography (OPT) for revealing the exact extent of bone alteration, the internal structure and the presence of sequestra and periosteal new bone [16].

**materials and methods**

Due to previous observation of 10 cases of jaw bone necrosis under long-term treatment with bisphosphonates in breast cancer patients [7], we considered two groups of patients. All the patients complaining of odontostomatological symptoms potentially related to the development of jaw bone necrosis who were under bisphosphonate treatment or have previously received bisphosphonates, underwent maxillary CT scan and maxillo-surgeon clinical examination. Asymptomatic patients who were under bisphosphonate treatment were asked to perform a standard OPT.

From February 2005 to October 2005, five patients who complained of symptoms eventually related to jaw bone necrosis performed maxillary CT scan, and maxillo-surgeon evaluation; two patients, with a wide area of exposed bone also underwent a jaw biopsy as a completion of diagnosis.

In the same time interval, panoramic radiographs (OPT) were collected from 76 asymptomatic patients. In this group, median range of treatment with bisphosphonate was 20 months (3–97 months). All the OPTs performed were revised by an internal radiologist with the aim of identifying bone alterations that may reflect or be similar to those usually observed in avascular bone necrosis. Patients with radiological features of suspicious lesions, were asked to perform a maxillary CT scan in our Institution and eventually a bone biopsy.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Pts with evidence</th>
<th>Pts within normal range</th>
<th>Pts with suspect</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Patients observed</td>
<td>5</td>
<td>73</td>
<td>3</td>
<td>81</td>
</tr>
<tr>
<td>Age at starting BPH, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
<td>55</td>
<td>47</td>
<td>54</td>
</tr>
<tr>
<td>Range</td>
<td>42–61</td>
<td>31–82</td>
<td>44–47</td>
<td>31–82</td>
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<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre</td>
<td>0</td>
<td>31</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Post</td>
<td>4</td>
<td>42</td>
<td>3</td>
<td>49</td>
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<td>UK</td>
<td>1</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Concomitant treatments</td>
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<tr>
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<td>1</td>
<td>23</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>CT only</td>
<td>3</td>
<td>34</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>Trastuzumab only</td>
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<td>2</td>
<td>0</td>
<td>2</td>
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<tr>
<td>CT+HT</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
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<tr>
<td>CT+Trastuzumab</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>No treatment</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Numbers of treatments with BPH</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
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<td>20</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Range</td>
<td>5–47</td>
<td>3–97+</td>
<td>9–29</td>
<td>3–97+</td>
</tr>
</tbody>
</table>

All CT exams were performed using the same multidetector unit (GE Light Speed CT16) with the same technical parameters (1.25 mm slice thickness, 0.6 mm increment, 9.38 mm/rot speed).

All the patients had breast cancer metastatic to the bone (characteristics of patients are listed in Table 1).

**results**

Five patients who were complaining of odonto-stomatological symptoms were referred to maxillo-surgeon, and received maxillary CT scan.

In this group, one patient, in treatment with endocrinotherapy for advanced breast cancer, received bisphosphonates for about 1 year. After tooth extraction, she developed suspicious mandibular necrosis around 3 months after the last administration of zoledronic acid (Figure 1). She subsequently underwent jaw biopsy and the histopathological diagnosis confirmed the suspicion of jaw necrosis. Her quality of life was severely affected from local pain and difficulties in eating. She received antibiotic therapy without clinical benefit, and no radiological improvement was detected by following CT scan. She died of lepto-meningeal progression 9 months afterwards.

The second patient developed symptoms (right mandibular pain) around 2 years after the first bisphosphonate administration, while on treatment with exemestane for her neoplastic condition. Zoledronic acid was discontinued, after the observation of a suspicious mandibular necrosis at maxillary CT scan. Following mandibular CT scan showed a progression of the lytic alterations, which clinically was reflected by the persistence of mild pain in the right mandible.

The third patient had been receiving zoledronic acid for 9 months before complaining of recurrent dental abscesses.

![Figure 1](image)
after dental avulsion. Maxillary CT scan revealed a lytic area with periosteal reaction in the right mandibular inferior bone, and clinical examination showed an area of exposed bone. The patient received intermittent antibiotic therapy with partial benefit. At that time, she was under chemotherapy treatment for her neoplastic condition. The lesion was stable in the follow-up CT scan. Nine months later, she died of liver progressive disease.

The fourth patient received bisphosphonates for nearly 4 years. She underwent right superior mandibular sequestrectomy for dental abscess after 2 years of bisphosphonate treatment. Since then she complained of recurrent dental infections and she performed a right inferior sequestrectomy 1 year after the previous one, and a left inferior sequestrectomy 2 years later, without clinical benefit. Pamidronate treatment was discontinued after the appearance of osteolytic lesion in a standard OPT. She then underwent a maxillary CT scan with the evidence of a wide osteolytic area in the inferior left jaw. Clinical examination confirmed a local condition attributable to mandibular necrosis. At the time of radiological diagnosis, the patient was receiving chemotherapy for her neoplastic condition.

The last patient received zoledronic acid for 3 years, and discontinued the treatment after the occurrence of symptoms including pain in the right upper jaw and nasal water swelling while drinking, in a site of tooth extraction about one year earlier. At that time, the patient was under chemotherapy for her breast tumours. The maxillary CT scan showed suspect upper right alveolar ridge bisphosphonates related vascular necrosis with oro-sinusal communication and the complete obliteration of the maxillary sinus with thickening of the sinus walls due to the presence of chronic sinusitis tissue in the highmore antrum (Figures 2 and 3). She then underwent upper jawbone biopsy and application of hemostatic mesh to seal the hole. Biopsy of the involved area showed fragments of fibro-vascular tissue and cortical bone characterized by active exudative abscessual and necrotizing chronic inflammation.

None of these patients had predisposing concomitant local or systemic diseases (such as diabetes), or were under chronic steroid therapy.

Considering asymptomatic patients, three out of the 76 OPTs revised, showed radiological features of suspicious jaw necrosis, revealing sclerotic regions of mandibular bone expression of sclerosing osteitis associated with peri-apical inflammatory lesions of regional teeth in two patients, and with the presence of two dental implants in the third. CT examinations confirmed the presence of mandibular alterations in all patients showing signs of periosteal reaction in one patient (Figure 4). One patient was under bisphosphonate treatment for more than 2 years, one patient for 13 months and one patient for 10 months. At the time OPT was performed, two patients were under chemotherapy, and one patient endocrine-therapy.
All the patients, according to clinical judgement, discontinued bisphosphonates treatment.

All the three patients underwent maxillo-surgeon evaluation and two of them were selected for bone biopsy with transcutaneous access. The surgical procedure was affected by severe pain in both cases. In spite of the sterility of the approach, one out of the two patients experienced post-operative soft tissue infection treated with abscess drain and antibiotic therapy. Because of the complications occurring in the first two patients, we decided not to perform any other biopsy procedure in the third eligible patient. In the first case the specimen harvested was a cortical bone sliver histopathologically normal, because the mobility of the mandible and the thickness of the cortical bone hampered the penetration of the needle into the marrow bone. In the second case no specimen was harvested due to the pain experienced by the patient.

All the three patients repeated maxillary CT scan after an interval of 4–5 months and confirmed the suspicious lesions substantially unchanged compared to previous exams. In these patients, bisphosphonates treatment wasn’t reconsidered due to the absence of clinical or radiological bone progression.

discussion
Pathogenesis of mandibular bone necrosis associated with bisphosphonates is unclear. Recently an analogy with ‘phossy jaw’ has been reported, suggesting a potential alteration in the normal phosphorus and calcium metabolism in these patients. This occupational historical disease (19th century) was caused by exposure to white phosphorus during the manufacture of matches. It was considered the most distressing of all the occupational diseases because it was very painful, and it usually led to patient’s disfigurement [17–18]. Persistence of hypercalcemia and eventually secondary hyperparathyroidism may predispose to the development of this condition [19].

Pamidronate and zoledronic acid are nitrogen containing bisphosphonates and are known to bind preferentially to sites of active bone resorption, exerting direct effects on osteoclastic activity through different mechanisms, including cytoskeleton changes and decreased liposomal function. These compounds may also directly induce osteoclast apoptosis [20].

Normal osteoclasts is vital to bone turnover while its effective inhibition halts bone resorption leading to accumulation of non vital osteocytes, microfractures of old mineral matrix and bone necrosis. The selective appearance of this process in the jaw, may be due to the specific anatomical pattern, of harboring teeth, thus uniquely exposing this part of the skeleton directly to the open environment and to continuous trauma due to mastication or to odontostomatological interventions. The antiangiogenic effect attributed to bisphosphonates might play a role, together with microtrauma, inflammation and chronic infection, in causing ischemic changes [21–24].

In our experience, the development of jaw bone necrosis in breast cancer patients seems to be higher than in other reports (incidence of about 6%). Four out of five patients had undergone invasive odontostomatological procedures during bisphosphonate treatment. The diagnosis was clinical and radiological, and in two patients with a widely-exposed jaw, a confirmatory bone biopsy was performed.

Three out of the 76 OPTs performed in asymptomatic patients, revealed radiological features of suspicious mandibular necrosis. Maxillary CT confirmed the presence of a sclerotic area with signs of periosteal reaction. All the three patients were referred to maxillo-surgeon and two out of three patients underwent mandibular biopsy, but histopathological results were not conclusive. Balancing the individual risk and benefit, we decided to discontinue bisphosphonate treatment in these patients, and the planned control maxillary CT scan showed no progression of the radiological findings. Patients remained asymptomatic. We do not know how these radiological modifications should be considered. Biopsy of the suspicious area was invasive and inconclusive. On the other hand, performing standard OPT is a simple procedure, and may allow identification of periodontal diseases or other conditions that in some way can predispose to the development of this uncommon event. Therefore the cure of potential infective foci prior to bisphosphonates administration, and the education of patients to absolutely avoid dental invasive procedure, may lead to a reduction in the incidence of this rare complication.

conclusion
In our routine activity, all the patients eligible for bisphosphonate therapy, before first administration, perform a standard OPT and clinical examination with treatment of potential infective foci. OPT is repeated every 6–8 months, and invasive odontostomatological procedures are completely avoided during therapy.

The benefits of bisphosphonates in patients with bone metastases from breast, prostate cancer and multiple myeloma are undoubted in terms of reduction of skeletal events and improvement in performance status and eventually in pain control. Anyway, long-term routine use of these drugs should take into account the potential occurrence of this relatively uncommon event.

references