

## Osteonecrosis of the jaw as an adverse bisphosphonate event: Three cases of bone metastatic prostate cancer patients treated with zoledronic acid

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### ABSTRACT

Bisphosphonates offer a significant improvement in the quality of life for cancer patients; these potent inhibitors of bone resorption have been shown to markedly reduce the morbidity frequently resulting from bone metastases. Despite the success of bisphosphonates as therapeutic agents, however, toxicity in the form of osteonecrosis of the jaw (ONJ) is a rare complication whose incidence rate has climbed in recent years. ONJ is defined as an unexpected development of necrotic bone in the oral cavity, and is commonly associated with administration of the bisphosphonates Pamidronate and Zoledronate. Clinical features include local pain, soft-tissue swelling, and/or loose teeth; ONJ is also often correlated with previous dental procedures, such as tooth extractions, during bisphosphonate therapy. Although additional risk factors--such as corticosteroids, chemotherapy, radiotherapy, trauma or infection—exhibit etiological associations with ONJ, the real pathobiology has not yet been fully elucidated. Here we report our findings on all 2005 ONJ cases presented at our institution resulting from bone metastatic prostate cancer treated with zoledronic acid. The incidence of ONJ is nearly 3% (3 out of 104) in these patients.

**Key words:** Bone metastasis, prostate cancer, osteonecrosis of the jaw (ONJ), bisphosphonates, zoledronic acid, skeletal-related events.

### INTRODUCTION

The skeleton is the most common site to be affected by metastatic cancers. Multiple myeloma, breast, and prostate cancers harbor the highest prevalence of bone metastases. While overall survival and lifespan of these patients is relatively long, they unfortunately carry a considerable morbidity due to skeletal-related events (SRE). These SRE include bone pain, general weakness/fatigue, impaired mobility, pathological fractures, spinal cord compression, and hypercalcemia, all of which contribute to a decreased quality of life. (1)

Metastases to the bone are common and difficult complications of prostate cancer; 80% of patients with advanced prostate cancer present with bone metastases. Median survival in patients with limited bone disease is over 53 months, 30

months in patients with visceral disease, and only 12 months in those with poor performance status and visceral disease. The rapid and severe manner in which bone metastases descend upon a patient's health commands attention for the clinical management of treatment options. (2, 3)

Palliative bone-targeted therapies are designed to prevent bone-pain, disability from cord compression, and pathological fractures. There are several approaches to the treatment of bone metastases: anticancer (endocrine or cytotoxic) treatment, external beam radiotherapy, palliative surgery, analgesia, and bisphosphonates. (1)

Bisphosphonates have emerged as an integral tool in the prevention of SRE in metastatic cancer patients. These compounds have a common phosphorus-carbon-phosphorus backbone and an affinity for hydroxyapatite crystals located

specifically in areas of dynamic bone resorption and regeneration. Through this targeted activity, bisphosphonates inhibit normal and pathological osteoclast-mediated bone resorption by multiple mechanisms; they reduce the number and activity of the osteoclasts by modifying their adhesion, recruitment, cytoskeletal arrangement, differentiation, and survival, and can also act through several mechanisms on osteoblasts and macrophages (4). Prostate cancer bone metastases differ from bone metastases associated with most other cancers because the former are usually sclerotic or osteoblastic. Osteoblastic metastases from prostate cancer increase osteoblast number and activity, bone volume, and bone mineralization rate; however, biochemical and microscopic evidence suggests that prostate cancer bone metastases, as in myelomas and breast cancers, have an osteolytic component. Furthermore, osteoclast number and activity are increased in prostate cancer-related osteoblastic metastases as well as in adjacent and distant healthy bone. (3, 5)

The overall effect of bisphosphonate treatment is thus the collective reduction of excessive bone turnover, resulting in preservation of structure and mineralization of the bone. Due to these findings, bisphosphonates have become the standard treatment for preventing skeletal complications in cancer patients with bone metastases. (3)

Zoledronic acid is the only bisphosphonate that has shown a statistically significant reduction in SRE, resulting in durable palliation of bone pain in prostate cancer metastases. (2) Although the optimal treatment duration of zoledronic acid therapy has not yet been established, available evidence suggests that bone morbidity is decreased as long as the patient undergoes zoledronic acid treatment. On the basis of clinical practice guidelines for breast cancer and multiple myeloma (5), zoledronic acid treatment should continue until the appearance of treatment-related adverse events or until a substantial decline in patient performance status is observed. (6)

Adverse effects associated with the use of bisphosphonates are rare and consist of pyrexia, renal function impairment, and hypocalcemia. Recently, a new complication associated with their use has been described: avascular osteonecrosis of the jaw (ONJ). (7) Here we describe three cases of ONJ in prostate cancer patients treated with zoledronic acid in a prospective surveillance report during 2005 at our hospital.

## CLINICAL CASES

A summary of the clinical cases is shown in table 1.

### Case 1.

A 60-year-old man affected by diabetes mellitus and ischemic cardiopathy was diagnosed of prostatic adenocarcinoma in 2000. We treated him with complete androgen blockade (bicalutamide + triptoreline) until serologic and retroperitoneal progression in October 2003. Retroperitoneal radiotherapy was administered, followed by a stramustine and triptoreline combination. He developed bone progression in December 2004. As the tumor became hormone refractory, he received chemotherapy and mensual zoledronic acid (4

mg. in 15 minutes, every 4 weeks). Since then he has undergone three additional chemotherapy treatments. Zoledronic acid was administered every four weeks for a total of 14 times. In December 2005 the patient presented dysesthesias of the jaw. Exploration of the oral cavity revealed halitosis, hypoesthesia of the inferior alveolar nerve, and soft-tissue swelling in the left hemiarch. An orthopantomography showed sequestrum formation related to osteonecrosis of the jaw (see figure 1).



Fig. 1. Orthopantomography of the ONJ developed in case 1 (left side).

### Case 2.

A 68-year-old man was diagnosed of prostatic adenocarcinoma in 2002 with bone metastases. He received palliative radiotherapy on vertebral collapses (D5-D8 and L3-L4). We prescribed complete androgen blockade (bicalutamide + gosereline) until the tumor became hormone refractory in September 2004. At this stage he was treated with chemotherapy while maintaining a good performance status. He then followed treatment with prednisone in monotherapy. Due to maxillae teeth infections, he underwent dental extractions before ONJ diagnosis. Zoledronic acid was administered for 8 courses and stopped when dysesthesias of the jaw, halitosis and fall of teeth occurred. Exploration of the oral cavity revealed loose teeth in the jaw, bone exposure, and adjacent soft tissue abscess. We performed an orthopantomography as a complementary diagnostic test (see figure 2).



Fig. 2. Orthopantomography of the ONJ developed in case 2. (right side).

### Case 3

A 70-year-old man was diagnosed with prostate adenocarcinoma in 1998. Radical intention radiotherapy was administered, followed by maximum androgen blockade (flutamide + triptoreline) until serologic and bone progression in July 2003. He received four chemotherapy lines and 12 doses of zoledronic acid. Tooth extractions were performed during zoledronic therapy. We interrupted bisphosphonate administration when pain and fall of teeth appeared. Exploration of the oral cavity revealed loose teeth in the mandible, bone exposure, and soft tissue swelling. An orthopantomography and CT of the jaw confirmed ONJ (see figure 3 and 4).



**Fig. 3.** Axial CT scan showing a diffuse osteonecrotic process involving part of the mandible, with gross bone destruction and an extensive periosteal reaction (case 3).



**Fig. 4.** Orthopantomography of the ONJ developed in case 3. (left side).

### DISCUSSION

The four types of intravenous bisphosphonates (clodronate, ibandronate, pamidronate and zoledronate) have shown therapeutic efficacy in the prevention of SRE related to the presence of bone metastases in breast cancer; (1) however, these drugs are not all effective for the treatment of bone metastases in prostate cancer. Several studies, which used pain due to bone metastases as the primary endpoint, failed to demonstrate a difference between clodronate and pamidronate treatment versus the placebo. (8, 9)

Zoledronic acid is the only bisphosphonate that has demonstrated a statistically significant reduction in SRE compared with placebo in patients with metastatic prostate cancer. As a result, it has become the standard treatment for this class of patients. (2)

Severe adverse effects associated with the use of intravenous bisphosphonates are uncommon; the most frequently reported side effects include fever, acute systemic inflammatory reactions, ocular complications, nephrotoxicity, and/or electrolyte abnormalities such as hypocalcemia, hypophosphatemia and hypomagnesemia. (10) In our series, only a low level hypocalcemia and a limited renal impairment were recorded in one and two patients, respectively (see table 1). Recently, a novel complication associated with the use of bisphosphonates has been described, known as avascular osteonecrosis of the jaw (ONJ). ONJ diagnosis is suspected in patients from the presence of such symptoms as pain, halitosis, soft-tissue swelling, gingival bleeding and infection, tooth loss, and/or dysesthesias of the jaw. (11-13) The typical presentation is a nonhealing extraction socket or exposed jawbone with progression to sequestrum formation, localized swelling, and purulent discharge. Multiple affected sites are frequent. (14) Laboratory analysis reveals normal oral-cavity flora and *Actinomyces* as the most commonly isolated organisms in the oral cavity of these patients. Radiographs routinely showed regions of mottled bone, due to sequestrum formation. (15) Tissue biopsy should be performed only if metastatic disease is suspected. In our patients, osteolysis consistent with bone loss could be observed in every orthopantomography.

To date, more than 200 cases of ONJ have been published since 2003, most often in multiple myeloma and breast cancer. (16) One of the first attempts to determine the incidence of ONJ was reported by Durie et al; the authors performed a web-based survey of 1203 patients with multiple myeloma and breast cancer receiving bisphosphonates and found an incidence of 12,9% (152/1203). (7) This series has been criticized, however, because it used an open, uncontrolled questionnaire that physicians could answer for their patients, and because the study included patients with either confirmed or only suspected ONJ. In another smaller but prospective study by Bamias et al, the global incidence of osteonecrosis of the jaw was found to be 6,7% (17/252) for the whole sample; 9,9% of patients with multiple myeloma, 2,9% with breast cancer, and 6,5% with prostate cancer. (11) We reported here three cases of ONJ in patients with prostate adenocarcinoma that received zoledronic acid in 2005 at our hospital. Our incidence in this period was near 3% (3/104).

**Table 1.** Main characteristics of the three clinical cases reported.

	<b>CASE 1</b>	<b>CASE 2</b>	<b>CASE 3</b>
AGE	60	68	70
RADIOTHERAPY	Retroperitoneal	Vertebral collapses	Radical intention on prostate
CHEMOTHERAPY	<ul style="list-style-type: none"> <li>• Stramustine.</li> <li>• Docetaxel + prednisone.</li> <li>• Vinorelbine.</li> </ul>	<ul style="list-style-type: none"> <li>• Docetaxel + stramustine.</li> <li>• Prednisone.</li> </ul>	<ul style="list-style-type: none"> <li>• Docetaxel + stramustine.</li> <li>• Clinical trial.</li> <li>• Vinorelbine.</li> <li>• Paclitaxel.</li> </ul>
CORTICOID THERAPY	YES	YES	NO
DESNUTRITION	Slight	Moderate	Slight
TEETH INFECTION	NO	YES	YES
CICLES OF BIFOSFONATES	14	8	12
HYPOCALCEMIA	NO	YES (minimum plasma level of 7,5 mg/dl)	NO
RENAL DISFUNCTION	Maximun serum creatinine level of 1,5	NO	Maximun serum creatinine level of 1,45

**Table 2.** Several suggested recommendations to prevent ONJ related to biphosphonates employment.

Assessment of dental status before treatment with bisphosphonates
Close monitoring of oral hygiene
Avoid invasive dental procedures during the treatment with bisphosphonates
Follow-up patients being treated with bisphosphonates during more than two years

Moreover, these studies assessed the characteristics and risk factors for the development of ONJ in patients treated with bisphosphonates. Among these, the duration of treatment and number of infusions were strongly associated, implicating drug exposure as the most significant risk factor for the development of osteonecrosis. In the study conducted by Bamias et al, no patients received fewer than 13 treatments, with a median of 35 infusions (range 13 to 68 infusions) (11). Our patients were also heavily exposed to zoledronic acid with a mean of 11,3 courses.

The type of bisphosphonate may play a role in the development of ONJ. For instance, some studies have observed fewer incidences of ONJ with pamidronate alone, indicating that osteonecrosis might occur earlier in treatment with zoledronic acid. (7, 17, 18) The reason for this difference remains unknown, but one possible explanation is that zoledronate has a more potent inhibitory effect on bone turnover than pamidronate. (11)

On the other hand, it has been postulated that dental procedures may be an initiator factor for ONJ. In Bamias et al, 88% of patients had been subjected to either dental extraction within the year or had dentures preceding ONJ diagnosis. (11) In parallel, two patients from our series had suffered from dental procedures in the previous year.

Treatment of patients with bisphosphonates-related osteonecrosis remains extremely difficult. Cessation of treatment could be considered in severe cases, but this option has not been shown to improve patient condition. Conservative therapy with antibiotics and mouth rinses is advocated, but a small percentage of patients require surgery, which can range from simple debridement or curettage to radical resection depending on the extent of necrosis. (19) Serious caution must be exercised when contemplating surgery, however, as it is possible to exacerbate the avascular process and worsen the patient's condition. In our series, one of our patients required curettage while we were able to manage the others with more conservative approaches. Other approaches such as hyperbaric oxygen therapy have not shown positive results. (12, 20, 21)

There are several ways to prevent osteonecrosis of the jaw in relation to the use of bisphosphonates, shown in table 2. Collaborations between medical oncologists and dentists are essential in order to minimize the morbidity of bisphosphonate-associated osteonecrosis. (17, 22, 23)

In conclusion, zoledronic acid is the most effective bisphosphonate in preventing skeletal related events, particularly bone pain in bone metastatic cancer patients. Unfortunately ONJ has emerged as a severe complication for patients undergoing a heavy treatment regimen. Although published literature on this issue is sparse, physicians should be alert to patients with multiple bisphosphonate therapies and/or those with a particular type of dental history. The evidence linking bisphosphonates to ONJ is considered as level V evidence (evidence that is provided only from case reports and clinical examples); prospective clinical trials are imperative in order to evaluate the true frequency of bisphosphonate-related ONJ and to establish the causal factors related to its incidence in cancer patients. (24)

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