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Bisphosphonate-induced osteonecrosis of the jaw in patients with bone metastatic, hormone-sensitive prostate cancer. Risk factors and prevention strategies

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ABSTRACT

Aims and background. Evidence from the literature suggests that osteonecrosis of the jaw is emerging as a serious complication of treatment with bisphosphonates for patients with advanced prostate cancer.

Methods and study design. This study is a series of 60 patients with osseous metastases from prostate cancer under complete androgen deprivation therapy. All patients also received bisphosphonates intravenously every 3 to 4 weeks. Over a period of 3 and a half years, we recorded the incidence, presenting signs and symptoms of osteonecrosis of the jaw among those patients and the diagnostic workup required.

Results. Nine of the 60 patients with metastatic prostate cancer were found to be affected with osteonecrosis of the jaw secondary to bisphosphonate administration at the Urology Department at the University Hospital of Alexandroupolis between January 2006 and August 2009. For diagnostic reasons, all 9 patients underwent computed tomography scan and magnetic resonance imaging of the maxillary region, as well as a three-phase whole body bone scan.

Conclusions. There is evidence that administration of bisphosphonates in patients with advanced prostate cancer may increase the risk of osteonecrosis of the jaw. Guidelines regarding the diagnosis and management of those patients are needed.

Introduction

Androgen deprivation therapy is currently considered the mainstay of treatment for locally advanced and metastatic prostate cancer (MPC). However, both the direct tumor involvement on bone in cases of metastatic lesions and the osteoporotic effects of androgen deprivation therapy result in a continuous decline in bone mineral density and an increased risk of osteoporosis, pathological fractures and other skeletal-related events[1]. The role of biphosphonates in the maintenance of bone health and prevention of skeletal complications in patients with advanced prostate cancer is well-defined. Biphosphonate-induced osteonecrosis of the jaw (ONJ) in patients treated for metastatic prostate cancer represents a recently recognized adverse effect of therapy[2,3].

The purpose of the present study was to estimate the incidence of ONJ in a population of patients with hormone-sensitive locally advanced and metastatic prostate cancer and to evaluate the usual presenting signs and symptoms of this condition.

Materials and methods

Sixty patients with MPC treated with complete androgen blockade were prospectively evaluated for the occurrence of ONJ. All patients with evidence of locally ad-

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vanced and/or MPC under complete androgen blockade received periodic infusions of zoledronic acid (Zometa®, Novartis, Varese, Italy). Zoledronic acid was given intravenously every 3 to 4 weeks in doses of 3 or 4 mg, depending on the estimated glomerular filtration rate of each patient. We studied the incidence and characteristics of cases with ONJ who were diagnosed among these patients between January 2006 and August 2009.

Every patient that entered the zoledronic acid scheme and prior to initiation of treatment was given a thorough dental examination and was asked to refrain from dental procedures after the initiation of therapy. All patients were then re-examined at 3-month intervals by the same maxillofacial surgeon. In the MPC patients, bone scanning with 925 MBq ^{99m}Tc-methyldiphosphate (MDP) revealed the presence of bone metastatic lesions in all 60 patients. Parameters such as the presence and location of bone metastases, the duration of zoledronic acid infusions, and the mean cumulative dose of the drug in relation to the occurrence of ONJ were also recorded. After evaluating these parameters, an attempt was made to identify risk factors for the development of ONJ among patients treated with zoledronic acid infusions for the treatment of advanced prostate cancer.

Results

From January 2006 until August 2009, 9 cases of ONJ were diagnosed among 60 patients with MPC treated with zoledronic acid. The median duration of therapy with zoledronic acid was 22 months at the time of diagnosis, and the mean cumulative dose was 72 mg (range, 36-88). Despite surgical intervention, antibiotic therapy, and topical use of chemotherapeutic mouth rinses, the lesions did not completely respond to therapy. Moreover, discontinuation of biphosphonate administration did not result in healing.

Presenting signs and symptoms of ONJ in addition to exposed bone were: asymptomatic, discovered during routine dental examination in 2 (22.2%) cases, pain in 6 (66.6%) cases, and mobile teeth (11.1%). With regard to the location of the lesions, 7 (77.7%) occurred in the mandible alone and 2 (22.3%) in the maxilla. Dental comorbidities included the presence of periodontitis in 6 patients (66.6%), abscessed teeth in 1 patient (11.1%), root canal treatments 2 patients (22.2%), and the presence of mandibular tori in 1 patient (11.1%). The precipitating event that led to bone exposure was tooth removal in 2 patient (22.3%), advanced periodontitis in 3 patients (33.3%), periodontal surgery in 1 patient (11.1%), dental implants in 1 patient (11.1%), root canal surgery in 1 patient (11.1%), and spontaneous exposure in 1 patient (11.1%).

The median number of treatment cycles and time of exposure to bisphosphonates were 37 infusions and 25.3 months for patients with ONJ compared with 18 infusions and 13 months, respectively, for patients with no evidence of ONJ. The incidence of ONJ correlated with the presence of extended bone involvement, as all 9 patients had bone metastases in their baseline radionuclide studies. However, none had metastatic lesions in the mandible or maxilla. Seven of 9 (22.2%) patients with ONJ had a history of dental procedures within the last year or use of dentures.

For diagnostic reasons, all 9 patients underwent a computed tomography (CT) scan and magnetic resonance imaging (MRI) of the maxillary region, as well as a 3-phase whole body bone scan. Three-phase bone-scintigraphy showed increased perfusion and an increased blood pooling at the maxillary lesion in all patients at the metabolic phase (Figure 1). Whole-body scintigraphy showed remote and bone metastases in all patients. CT and MRI showed anomalies in all patients. Under CT, both cortical and trabecular bone aspects showed predominantly sclerotic regions and prominent osteolytic lesions in the jaws with periostal bone proliferation (Figure 2). MRI was negative for adjacent soft-tissue involvement but was suspicious for bone destruction (Figure 3). Clinical photographs of the lesions demonstrate the bony exposure and soft-tissue inflammation that we observed (Figure 4).

Discussion

Biphosphonates are the agents of choice for the treatment of osteoporosis and have proved useful for the

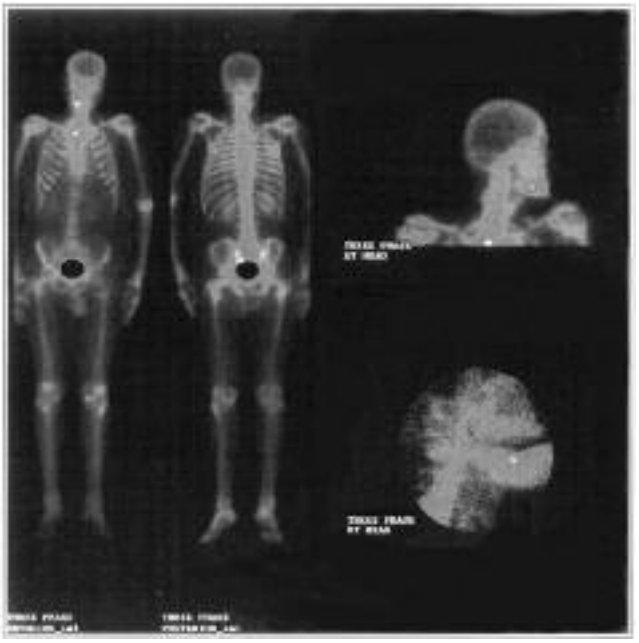

Figure 1 - Three-phase bone scan. Increase accumulation of ^{99m}Tc MDP on the right maxillary region.

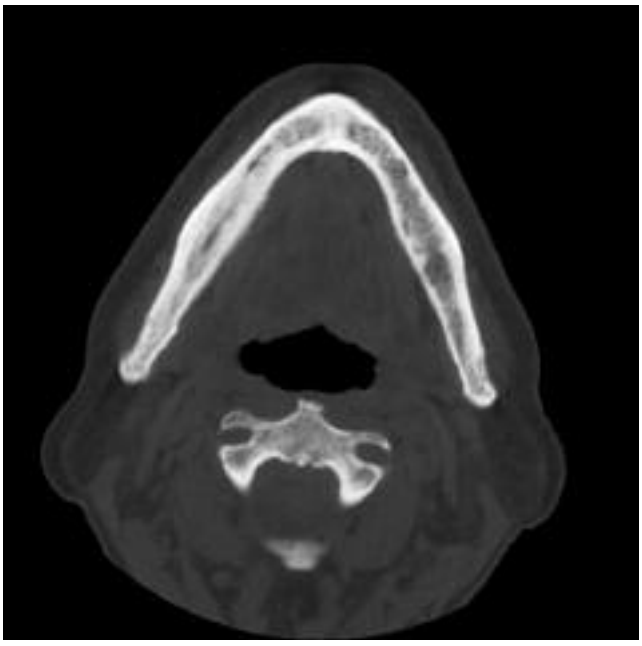

Figure 2 - Axial CT scan showing a osteosclerotic process in the right part of the jaw with extensive periosteal reaction.

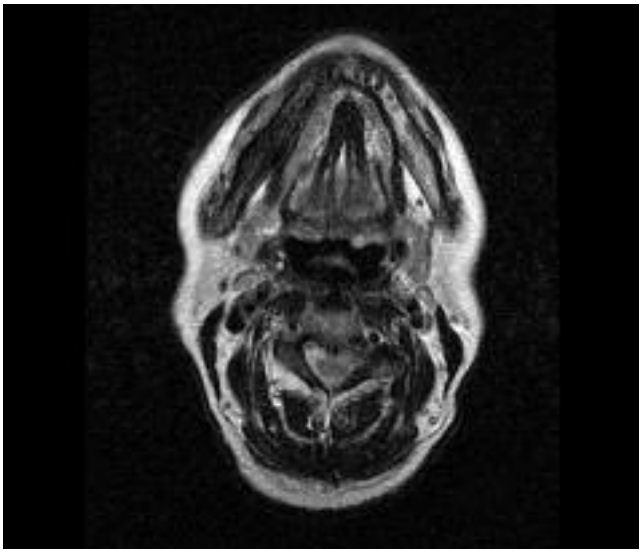

Figure 3 - MRI demonstrating osteonecrosis (low intensity on T2 weighted images) in the mandible of a patient with a history of having received zoledronic acid therapy.

prevention and management of complications associated with malignancies such as hypercalcemia and bone metastases from multiple myeloma, breast and prostate cancer, as they are highly active inhibitors of osteoclasts[4-6]. In normal bone homeostasis, osteoclastic resoption and osteoblastic bone disposition are well balanced. This balance is disrupted by the exogenous administration of bisphosphonates[7,8]. There is evidence that biphosphonates prevent, reduce, and delay cancer-

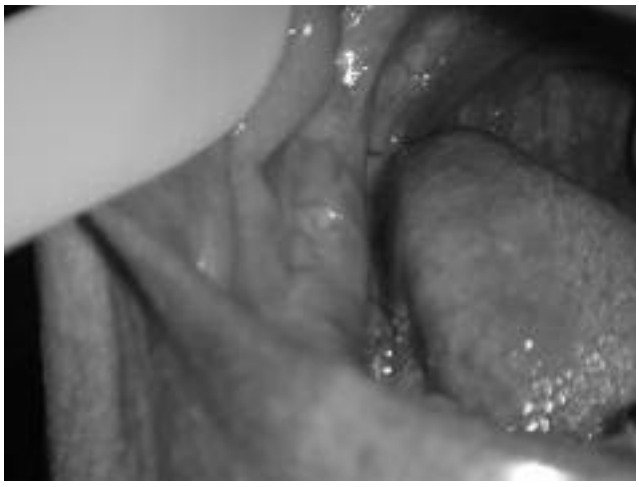

Figure 4 - Clinical photograph of a patient with osteonecrosis and a history of having received bisphosphonate therapy. Nonhealing extraction socket of nine months' duration in the lower right mandible of a patient with a history of metastatic prostate cancer who received zoledronic acid therapy.

related skeletal complications. They have substantially decreased the prevalence of such events since their introduction, thereby improving the quality of life for cancer patients[9,10].

Zoledronic acid is a third-generation, intravenous bisphosphonate formulation[11,12]. It is the only biphosphonate that has shown a statistically significant reduction in skeletal-related events[13]. The mechanisms of action of bisphosphonates are still being elucidated. These drugs are understood to hinder the resorption of bone by inhibiting osteoclastic activity. Hughes *et al.*[14] described inhibition of osteoclast development from monocytes, increased osteoclastic apoptosis (programmed cell death) and prevention of osteoclastic development from bone marrow precursors. Sato and Grasser[15] reported a reduction in osteoclastic activity through the effect of bisphosphonates on the cytoskeletal structure of the cell. Teronen *et al.*[16] presented an alternative theory of bisphosphonate action through its effects on down-regulation of matrix metalloproteinases. Vitte *et al.*[17] observed the stimulation of osteoclastic inhibitory factor synthesis by osteoblasts. Others have detected an antiangiogenic effect associated with bisphosphonates, whereas there is evidence that the drugs may have a direct antitumor effect by inducing apoptosis of tumor cells[18].

Biphosphonates can be divided into two categories: nitrogen-containing and non-nitrogen-containing[19]. Overall, biphosphonates are well-tolerated, and the most common adverse events are influenza-like syndrome, arthralgia, and when used orally, gastrointestinal symptoms, nephrotoxicity and electrolyte abnormalities[20]. The dose of biphosphonates may need to be adapted to renal function, and initial evaluation of creatinine clearance is advised. Biphosphonates can be

combined with radiation therapy and chemotherapy, and the additional administration of calcium and vitamin D is suggested but not considered mandatory.

ONJ is a rare complication of treatment with biphosphonates whose incidence has climbed in recent years. ONJ is defined as an unexpected development of necrotic bone in the oral cavity, commonly associated with administration of bisphosphonates, especially i.v formulations[10,21]. Nitrogen-containing more than the non-containing biphosphonates have been implicated in ONJ. Antimicrobial agents have an important place in the management of this type of osteonecrosis. Preventive strategies of ONJ should include good dental hygiene for all patients and completion of elective invasive dental procedures before initiating high-dose i.v. bisphosphonate therapy[4].

In a review of 1,203 patients, Durie *et al.*[22] reported 75 patients with ONJ, with a mean time to diagnosis of 18 months after initiation of therapy for those receiving zoledronic acid compared with 6 years for those receiving pamidronate. The study also identified a greater incidence of osteonecrosis among patients receiving zoledronic acid than that of patients receiving pamidronate[22].

Regarding diagnosis of ONJ, MRI has been shown to have a greater sensitivity than plain radiography in detecting asymptomatic bone disease, while providing both anatomic and physiologic information about bone marrow involvement. CT can be used to determine the presence or absence of bone destruction in cases where MRI is negative[23,24].

In patients with established ONJ, intermittent or continuous antibiotic treatment together with minimal surgical debridement can be beneficial. The goal of treatment is to prevent a secondary infection in the soft tissues and possibly osteomyelitis and also prevent pain. Good dental hygiene and the use of mouth rinses and chlorhexidine gels are just as important[25].

Srinivas and Colocci[26] concluded that treatment with biphosphonates is indicated in patients with prostate cancer and osteoporosis, but it may be considered in patients with osteopenia and/or additional risk factors. As the use of biphosphonates seems to be associated with the development of ONJ, it was observed that the length of exposure to biphosphonates seemed to be the most important risk factor. The type of biphosphonate used and the history of previous dental procedures were also considered important risk factors[27].

Marx[28] was the first to report a case series and concluded that amino-bisphosphonates, such as zoledronic acid, are the leading cause of avascular necrosis of the jaw. It was then proposed that bisphosphonates may cause necrosis as they inhibit osteoclasts[29,30].

In contrast, Guarneri *et al.*[31] in a study of 57 patients with bone metastases observed that ONJ occurred in only 5% of the examined population and therefore concluded that biphosphonates are safe even after prolonged administration.

García Sáenz *et al.*[10] agreed that adverse events related to the use of intravenous bisphosphonates are uncommon. Some studies indicated a lower incidence of ONJ when patients were treated with pamidronate alone, suggesting that osteonecrosis might occur earlier in patients under treatment with zoledronic acid[22,32].

Prevention and early identification of patients at risk for ONJ should be a primary concern. Patients should be instructed on the importance of maintaining good oral hygiene and regular dental assessments. Dentists and oral surgeons should, if possible, complete any necessary dental or jaw procedures before the initiation of zoledronic acid infusions. In cases where dental procedures must be undertaken during treatment with zoledronic acid, close coordination with a dental specialist is mandatory. In any case, efforts should be made not to postpone or interrupt the infusion scheme.

In conclusion, the benefits derived from the administration of bisphosphonates in patients with hormone-sensitive, locally advanced and metastatic prostate cancer should be weighed against the adverse effects, including the risk of ONJ. ^{99m}Tc-MDP three-phase bone scan could be used as a screening test to detect osteonecrosis, and CT scan and MRI are useful to define the features and extent of osteolytic lesions.

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