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Prevention of Osteonecrosis of the Jaw in Patients with Bone Metastases Treated with *Bis*phosphonates

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Abstract. *Bisphosphonates (BPs) are potent inhibitors of osteoclast-mediated bone resorption and are widely used in the treatment of bone metastases. Osteonecrosis of the jaw (ONJ) is the worst side-effect related to BP use. At our Center, we have implemented internal guidelines regarding the management of patients with bone metastases from solid tumors. Our analysis includes 200 patients affected by solid tumors with bone metastases who received zoledronic acid. They underwent a baseline mouth assessment to evaluate their dental conditions and to perform dental care; a dental follow-up was performed every six months. All patients received calcium and vitamin D daily. Dental examination and application of preventive measures led to a total reduction in ONJ in our patients treated with zoledronic acid. The keystone in management of ONJ is prevention, and the risk of developing ONJ during treatment with zoledronic acid is reduced by implementing preventive measures.*

Many types of cancer at an advanced stage progress to bone invasion. Bone metastases are associated with significant morbidity and mortality of the patient, due to bone fracture, hypercalcemia, spinal cord compression, and lead to bone surgery or radiation therapy (1-2). *Bis*phosphonates (BPs) are analogs of inorganic pyrophosphates, potent inhibitors of osteoclast-mediated bone resorption. They inhibit osteoclast function and therefore block the formation of 'punched-out' lytic bone lesions and consequent manifestation of lytic bone diseases (3). BPs have also been shown to inhibit tumor cell proliferation, angiogenesis, migration, and to activate immune responses (4-5). They have been widely used mostly in the treatment of metastatic disease and in the management of bone diseases, including hypercalcemia related to malignancy, myeloma-related bone disease, Paget's disease and osteoporosis. First introduced more than 20 years ago, BPs reduce pain and prolong the time for development of skeletal-related complications, such as fractures, vertebral compression and cord compression requiring radiation or surgery. BPs also reduce hypercalcemia and improve patients' quality of life and performance status; however, no consistent benefit in survival has been demonstrated with the use of these agents in patients with lytic or blastic bone disease (6-8). Since 2003, several reports have been published on the profile of adverse effects of this class of agents, highlighting the development of renal insufficiency, and especially of osteonecrosis of the jaw (ONJ), characterized mainly by exposed necrotic bone (9-13).

ONJ has an estimated incidence of 1%-12% among patients with cancer receiving high-dose intravenous BPs (14); this is a rare complication which affects a patient's quality of life in an extensive way. A definitive treatment for BP-associated ONJ has not yet been established. Oncologists must be aware of the clinical signs and symptoms, and of the recommendations for patient management, including prevention and early recognition (15). Screening of the oral cavity and dental care was suggested as mandatory preventive measures for ONJ in patients receiving BPs. The most important risk factors for the development of ONJ have been described, such as long-term exposure to BPs, the type of BP, older age, and dental procedures during the treatment (16, 17). At our Center, we have implemented internal guidelines in the management of patients with bone metastases from solid tumors, in order to prevent any kind of complication, particularly ONJ.

Patients and Methods

Our analysis includes a cohort of patients affected by solid tumors with bone metastases who received zoledronic acid since 2006 (Table I). Four groups of patients were established: those with breast

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cancer; with lung cancer; with prostate cancer; and with other types of cancer. Data were collected regarding malignancy, dental condition and the onset of ONJ. Patients with previous use of BPs without dental screening were excluded from the trial. A total of 200 patients with a mean (±SD) age of 68.3±3.9 years underwent a baseline mouth assessment (detailed examination and panoramic x-ray scans of the oral cavity) to detect potential dental diseases, and dental care, when required.

All patients underwent therapy with zoledronic acid at a dose of 4 mg every 28 days, plus daily calcium and vitamin D. Routine dental care, smoking habit, history of tooth extraction, use of dentures, and root canal therapy were recorded. The median dental follow-up (defined as the time between the first and last dental visit) was six months. All patients were informed about the possible complication of ONJ and instructed to avoid elective invasive dental procedures that might not heal completely prior to starting therapy. Patients were encouraged to stop smoking and to reduce their intake of alcohol. We performed a brief oral examination looking for open ulcers, swelling of soft tissues, drainage, exposed or necrotic bone, or non-healing of an extraction socket. Dental surveillance included a review of oral care, routine dental cleaning, examination of dentures, if any, and attention to avoiding soft tissue injury.

We calculated the number of patients developing dental disease by tumor type, separating the nonsmokers from the smokers, and evaluated the mean and standard deviation. The comparative study between smokers and nonsmokers in each tumor group and among the four tumor groups was based on analysis of variance (ANOVA). Statistical significance was considered for $p<0.05$

Table I. *Patients' characteristics*.

Patients (N)	200
Cancer type	
Breast	90
Lung	50
Prostate	50
Other (gastric, colon, bladder, thyroid)	10
Previous therapy	
Corticosteroids	Breast cancer: 70/90 Lung cancer: 50/50 Prostate cancer: 50/50 Other cancer: 2/10
Antiangiogenetics	Breast cancer: 30/90 Lung cancer: 5/50 Prostate cancer: 0 Other cancer: 0
Cyclophosphamide	Breast cancer: 90/90 Lung cancer: 0 Prostate cancer: 0 Other cancer: 0
Doxorubicin	Breast cancer: 20/90 Lung cancer: 0 Prostate cancer: 0 Other cancer: 1/10
Other patient features	
Smoker	Breast cancer: 30/90 Lung cancer: 20/50 Prostate cancer: 25/50 Other cancer: 5/10
Poor dental hygiene	Breast cancer: 20/90 Lung cancer: 10/50 Prostate cancer: 30/50 Other cancer: 2/10
Median administration of ZA (4 mg q 28)	20

Results

Following the described examination procedures in each case, none of the 200 patients treated with zolendronic acid developed ONJ. This suggests that the performance of dental examination and the application of preventive measures can lead to a sustained reduction in ONJ. When invasive dental procedures were necessary, BP use was interrupted for 3-7 months prior to the procedure (18-22) and treatment was resumed after oral healing.

In this regard, the Expert Panel recommended avoiding tooth extraction and instead recommended endodontic (root canal) therapy where appropriate (18). There is no consensus in literature on the discontinuation of BPs, because once these drugs are incorporated into the bone their half-life ranges across years. Considering that one of the most important risk factors for ONJ is the number of zoledronic acid infusions, we decided to stop therapy with zoledronic acid after two years of continuous treatment, and then to re-evaluate the patients by orthopantomography. Since poor oral health may be a significant risk factor for ONJ development, we have educated our patients on oral hygiene and inspected the oral cavity prior to each administration of BP.

We identified smoking as a risk factor for development of caries and tooth loss. Smoking patients reported a greater number of dental diseases (caried teeth and tooth loss) than non-smokers ($p<0.05$) (Figure 1). These differences are significant when comparing patients with the same type of tumor, while there are no differences due to the type of tumor ($p=0.99$).

Despite the increased risk of incurring dental disease in smokers, no patient developed ONJ as a result of the preventive approach and the close follow-up.

Discussion

According to the American Association of Oral and Maxillofacial Surgery guidelines (23), the onset of ONJ (stage 0) is characterized by chronic inflammation of the gums with scarce signs of healing after trauma, tooth extraction or surgery; the patient may develop paresthesia, odontalgia or lingual dysesthesia, loss of teeth, or periodontal fistula. Later stages (1 to 3) are characterized by bone and tissue necrosis, sometimes with fistula in the

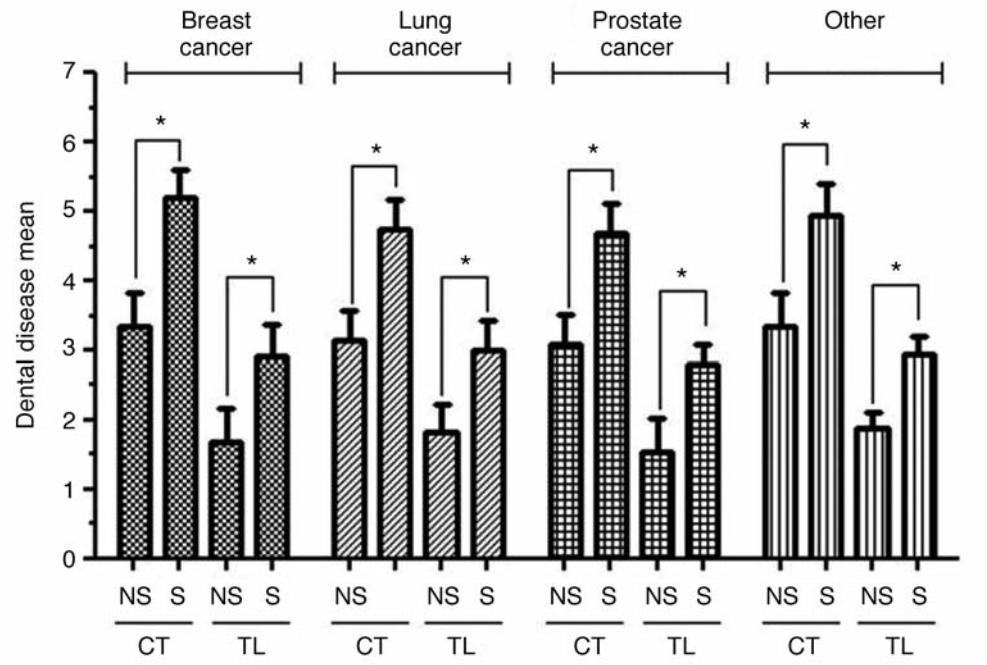

Figure 1. *Mean number of dental diseases (CT: Caried teeth; TL tooth loss) in non-smoker (NS) and smoker (S) patients grouped by cancer type. *Significant difference at p<0.05.*

oral cavity or externally to the skin and bleeding, pain and infection (24-26). The mechanism of BP-induced osteonecrosis is unclear, but it is probably related to severe suppression of bone turnover. Several predisposing or precipitating factors have been identified: periodontal disease, dentoalveolar surgery, poor oral hygiene, previous trauma, corticosteroid therapy, immunocompromised state with increased risk of infection, possible vascular insufficiency, underlying hypercoagulable state secondary to underlying malignancy (26), and non-malignant hematological disorder (anemia, thalassemia, sickle-cell trait/disease) (27). There is a positive statistically significant association with sequential intravenous treatment with pamidronate followed by zoledronic acid of rheumatoid-osteoarthritis, hypothyroidism, diabetes, and obesity. A negative association was identified with exposure to 5-fluorouracil, cyclophosphamide, doxorubicin, and methotrexate, but not antiangiogenic agents (bevacizumab). Most patients with ONJ had a history of prior dental or oral surgical manipulation, and only few patients have reported spontaneous ONJ (26). Beyond these aspects, genetic polymorphisms also influence the appearance of ONJ (27) and the diminution of bone remodelling during BP therapy. Furthermore, when constant micro-lesions are combined with the presence of a peculiar oral microflora, there can be a super-infection due to a particular poorly healing microenvironment in the maxilla, and this may contribute to ONJ (16, 17). Median time-to-development of this complication varies with the type of BP used for lytic bony disease, and it is relatively shorter with the more potent agents. During therapy with BPs, patients must immediately consult their dentist and oncologist in case of acute symptoms, pain, loosening teeth or abnormal smell. We have demonstrated that continuous surveillance of risk factors can reduce the incidence of ONJ during BP therapy.

Conclusion

The keystone in management of ONJ is its prevention. ONJ is a manageable and preventable condition, and the risk of development it during treatment with BPs can be reduced by implementing preventive measures. BP therapy was effective in palliation of pain in patients with bone metastases, and a multidisciplinary approach, including onco-hematologists and dental teams, were here demonstrated to be useful in preventing ONJ.

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