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Osteonecrosis of the jaw in patients treated with denosumab for metastatic tumors to the bone: A series of thirteen patients

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ABSTRACT

This case series describes the course of osteonecrosis of the jaw (ONJ) in thirteen patients with metastatic bone tumors treated solely with denosumab. Patients on denosumab may be more prone to developing ONJ even without a risk/precipitating factor and they may develop ONJ early in their denosumab therapy. The outcomes of ONJ in ten patients following a period of denosumab discontinuation after the onset of ONJ were: 3 had complete resolution of symptoms, 4 patients' ONJ progressed, 2 patients' ONJ was unchanged and in 1 patient there was partial ONJ resolution. The role of drug discontinuation prior to an invasive dental procedure or after the onset of ONJ still remains debatable.

1. Introduction

Metastatic bone disease is a relatively common event in the advanced stages of many malignancies (Hofbauer et al., 2014; Coleman, 2001). The most common cancers in men and women in the United States are prostate and breast cancers respectively (Siegel et al., 2015). Bone-modifying agents decrease the incidence of skeletal-related events (SREs) such as spinal cord compression, bone fracture, or surgery as well as the need for skeletal radiotherapy. The management of these cancers often necessitates the use of antihormonal therapies such as gonadotropin-releasing hormone (GnRH) agonists and aromatase inhibitors (AI), which are associated with increased bone resorption and skeletal fragility (Gralow et al., 2009; Coleman, 2001).

Bone modifying agents such as intravenous bisphosphonate (pamidronate and zoledronic acid) and denosumab are approved for prevention of SREs. Denosumab is a fully humanized monoclonal immunoglobulin antibody that disrupts the activation of receptors for nuclear factor kappa β ligand (RANKL) (Lewiecki, 2010; Boyle et al., 2003; Vij et al., 2009). It also inhibits the development and activation of osteoclasts by preventing the binding of RANKL to RANK, a transmembrane receptor that is expressed in the cell membranes of pre-osteoclasts and osteoclasts. This antibody therefore promotes osteoclast apoptosis that in turn decreases bone resorption and increases bone density. Denosumab was approved in 2010 by the FDA for the prevention of SREs in patients with bone metastases and in 2011 to prevent endocrine-therapy-induced bone loss in patients taking aromatase inhibitors for breast cancer and in patients with non-metastatic prostate cancer.

Various clinical trials have shown that denosumab may be more effective than zoledronic acid in the prevention of SREs in patients with metastatic bone disease (Stopeck et al., 2010; Henry et al., 2014; Fizazi et al., 2011; Lipton et al., 2012; Scagliotti et al., 2012; Sun and Yu, 2013). Denosumab is administered subcutaneously and cleared by the reticuloendothelial system, thereby preventing nephrotoxicity. The circulatory half-life of denosumab is 26 days, while the half-life of IVBP ranges from 10 to 12 years. Unlike intravenous bisphosphonate (IVBP), denosumab does not appear to accumulate in the bone. In addition, denosumab has been found to be more cost-effective in the prevention of SREs (Baron et al., 2011; Stopeck et al., 2012; Uyanne et al., 2014). Moreover, other studies stated otherwise (Xie et al., 2012, 2011). Patients on denosumab for metastatic bone disease receive 120 mg subcutaneously every 4 weeks while patients on denosumab for the management of osteoporosis/osteopenia or to increase bone mass receive 60 mg subcutaneously every 6 months.

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Osteonecrosis of the jaw (ONJ) is a well-known complication of antiresorptive medication such as IVBP and was initially termed bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Marx et al., 2005; Estilo et al., 2008b; Watters et al., 2013). With the advent of new classes of medication such as denosumab, sunitinib, bevacizumab and ipilimumab (recently described in a separate report) giving rise to a similar complication (Estilo et al., 2008a; Aghaloo et al., 2010; Fleissig et al., 2012; Otto et al., 2013; Pichardo et al., 2013; O'Halloran et al., 2014; Owosho et al., 2015), the condition is now more accurately named medication-related osteonecrosis of the jaw (MRONJ), reflecting the fact that it can be caused by various medication classes (Ruggiero et al., 2014). The AAOMS 2014 position paper describes MRONJ as an area of exposed bone or probed bone either intraorally or extraorally through a fistula of greater than 8 weeks duration in a patient with a history of antiresorptive medications and no history of radiation or metastatic tumor of the jaw (Ruggiero et al., 2014).

Cases of ONJ related to denosumab use were reported during randomized clinical trials for the treatment of patients with metastatic bone disease; the latter were case reports (Saad et al., 2012; Stopeck et al., 2016; Diz et al., 2012; Pichardo et al., 2013; Malan et al., 2012; Ohga et al., 2015; You et al., 2015; Olate et al., 2014; Qi et al., 2014; Fizazi et al., 2011, 2009; Henry et al., 2011; Lipton et al., 2007; Stopeck et al., 2010). In this study we describe a series of 13 cases of osteonecrosis of the jaw in patients treated with denosumab alone. We report the outcome of ONJ in 10 patients following a period of denosumab discontinuation (drug holiday).

2. Patients and methods

The study was approved by the Memorial Sloan Kettering Cancer Center (MSKCC) Institutional Review Board. Thirteen patients were referred to MSKCC's Dental Service by the institution's medical oncology service for evaluation of oral complaints such as exposed bone, jaw pain, non-healing extraction sites, and tooth mobility. All patients were treated with denosumab for management of metastatic bone tumors. No history of other antiresorptive agents was reported.

The following clinical information was reviewed: vital status; demographics; primary cancer diagnosis; site(s) of bone metastasis(es); history of chemotherapy; follow-up period (defined as time from onset of ONJ to last follow-up visit); history of active tobacco use; co-morbidities (active steroid use, diabetes mellitus and/or rheumatoid arthritis); site of ONJ lesion; precipitating factors for the development of ONJ; stage of ONJ at initial presentation, as defined by the American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaw (Ruggiero et al., 2014); number of doses of denosumab prescribed before the onset of ONJ; size of ONJ lesion(s) at diagnosis; drug discontinuation; duration of drug holiday (defined as the period of discontinuation of denosumab from ONJ diagnosis to last follow-up visit or resolution of ONJ); and the clinical outcome and size of ONJ at last follow-up visit following drug holiday. ONJ outcome was divided into four categories: resolution (complete mucosal coverage of prior exposed bone); partial resolution (reduction in size of exposed bone); no change and progression (increase in size of exposed bone).

3. Results

The summary of the characteristics of patients with denosumab-related ONJ is presented in Table 1. Thirteen patients (female n = 7, male n = 6; ages 49–82 years) presented with exposed bone in the jaw (Fig. 1A–D). All patients received 120 mg of denosumab subcutaneously every 4–6weeks. Twelve patients are Caucasian and one patient was of Asian descent. The primary cancer diagnoses are as follows: 6 patients with breast cancer, 6 patients with prostate cancer, and 1 patient with lung cancer. Bone metastases involved the spine, pelvis, femur, rib, sternum, and scapula, with the spine and pelvis affected more frequently. Seven patients had multiple bone metastases. All patients received either GnRH agonists or AI antihormonal therapy. As of last follow-up, 1 patient has died of disease.

Eight patients (Cases 1, 2, 4, 5, 6, 8, 9 and 11) had no history of smoking and no comorbidities (steroid use, diabetes mellitus and/or rheumatoid arthritis). Two patients (Cases 7 and 10) had no history of smoking and had used steroids. One patient (Case 12) was a diabetic with no history of smoking. One patient (Case 3) had a history of smoking and no comorbidities. One patient (Case 13) had a history of smoking and steroid use comorbidity.

Summary of the characteristics of ONJ in patients on denosumab are presented in Table 2. At ONJ onset, the number of doses of denosumab treatment ranged from 5 to 36 doses, with a median of 8 doses and mean of 15 doses. Ten (77%) cases of ONJ involved the mandible, and 4 cases involved the maxilla (one patient had ONJ in both maxilla and mandible). The areas of bone exposed at first clinical presentation ranged from 1 to 50 mm. Dental extractions were reported in 7 patients prior to ONJ onset. The remaining 6 patients denied a history of dental procedures prior to ONJ onset. Seven patients were considered to have stage 1 ONJ, and 6 patients had stage 2 ONJ at initial presentation. In those with history of dentoalveolar procedures, the time from dental extraction to the onset of ONJ ranged from 4 to 12 months. Patients with a history of dental extractions did not undergo a period of drug holiday prior to

Table 1
Summary of the characteristics of patients with denosumab-related ONJ.

Case no.	Age	Gender	Primary cancer diagnosis	Metastatic bone site	Active history of tobacco use/steroid use/diabetes mellitus/rheumatoid arthritis	Alive/Died of disease
1	73	M	Prostate cancer	Pelvis/Femur	No/No/No/No	Alive
2	74	M	Prostate cancer	Pelvis	No/No/No/No	Alive
3	69	F	Lung cancer	Spine/Pelvis/Scapula	46 pack years/No/No/No	Alive
4	63	M	Prostate cancer	Spine/Pelvis	No/No/No/No	Alive
5	68	F	Breast cancer	Sternum	No/No/No/No	Alive
6	57	F	Breast cancer	Spine	No/No/No/No	Alive
7	82	M	Prostate cancer	Spine	No/Yes/No/No	Alive
8	56	F	Breast cancer	Sternum	No/No/No/No	Alive
9	72	M	Prostate cancer	Spine	No/No/No/No	Died of disease
10	76	F	Breast cancer	Spine/Pelvis	No/Yes/No/No	Alive
11	56	M	Prostate cancer	Pelvis/Rib	No/No/No/No	Alive
12	49	F	Breast cancer	Spine/Sternum/Rib/Pelvis	No/No/Yes/No	Alive
13	57	F	Breast cancer	Spine/Sternum	10 pack years/Yes/No/No	Alive