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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.

Keywords

Denosumab; Osteonecrosis of the jaw; Metastatic bone disease

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

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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 10–12 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; Xie et al., 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.

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., 2015; 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; Fizazi et al., 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).

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).

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 (Figures 1A–D). All patients received 120 mg of denosumab subcutaneously every 4 – 6 weeks. 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 their procedure. However, 10 patients discontinued denosumab following ONJ diagnosis with median holiday duration of 5.5 months (range: 1 to 16 months).

All patients were conservatively managed with 0.12% chlorhexidine gluconate rinses 2 to 3 times per day. Antibiotics and pain medications were prescribed when indicated. All dental extractions were performed by outside dentists. The follow-up period ranged from 0 to 26 months, with a median of 2.5 months. There was no follow-up information at the time of this study for 2 recently diagnosed patients. One patient died of disease shortly after his initial dental consultation.

Three of 10 (30%) had complete resolution of symptoms with complete mucosal coverage after exfoliation of the necrotic bone (Cases 1, 4 and 6) (Figures 2A–B). In 4 patients (40%), ONJ progressed, as measured by an increase in the size of the exposed bone (Cases 5, 8, 10 and 11) (Figures 3A–B). In 2 patients the area of ONJ was unchanged. In 1 patient, there was partial ONJ resolution, as measured by a decrease in the area of exposed bone.

Discussion

In this article, we described 13 patients who developed ONJ while treated with denosumab for metastatic bone disease. The reported incidence of denosumab-related ONJ in patients with metastatic tumors ranges from 1% to 2% (Khan et al., 2015). In 3 Phase III trials comparing denosumab to zoledronic acid in patients with metastatic disease, the incidence of ONJ in patients on denosumab was 1.8% compared to 1.3% in patients taking zoledronic acid (Saad et al., 2012). In the same clinical trials (open label extension phase), the incidence of ONJ was 1.9% in patients on denosumab and 1.2% in patients taking zoledronic acid (Stopeck et al., 2015). In a recent meta-analysis of seven randomized controlled trials evaluating the risk of ONJ in cancer patients treated with denosumab, the overall incidence was 1.7% and there was a numerically increased risk of developing ONJ in patients taking denosumab compared to patients taking bisphosphonates (Qi et al., 2014). The risk of developing ONJ is significantly increased for patients with metastatic bone disease who receive antiresorptive therapy compared to patients receiving antiresorptive treatment for osteoporosis/osteopenia (Dodson, 2015). No patients enrolled in FREEDOM and ABCSG-18 trials receiving denosumab for the treatment of osteoporosis developed ONJ (Gnant et al., 2015; Cummings et al., 2009). This is most likely due to the dosage and scheduling. It has been observed that patients are more likely to develop ONJ earlier in their denosumab therapy compared to patients on IVBP. (You et al., 2015; Diz et al., 2012; Bamias et al., 2005). A similar trend was noticed in our series: patients received a median of 8 doses and an average of 15 doses of denosumab before the onset of ONJ.

Owing to denosumab's short (26-day) half-life, the fact that it does not accumulate in bone and that it is largely inert within 6 months after last administration, drug discontinuation in patients on denosumab either before an invasive dental procedure or after the development of ONJ has been suggested to help prevent the development of ONJ or encourage earlier resolution of ONJ (Damm and Jones, 2013; You et al., 2015; Baron et al., 2011; Ruggiero et al., 2014). In the same phase III trials, Saad et al. identified that patients on denosumab had a numerically earlier resolution of ONJ (40.4%) compared to patients on zoledronic acid (29.7%) at the same follow-up period (Saad et al., 2012).

In this series, resolution and complete mucosal coverage was achieved in three of ten (30%) patients. We observed that patients with spontaneous ONJ had earlier resolution of their lesion at 7 and 8 months compared to the extraction-related ONJ at 15 months. Other studies have reported resolution of ONJ after discontinuation of denosumab after 7, 11, 15, and 18 months (Taylor et al., 2010; Malan et al., 2012; Ohga et al., 2015). In our series, however, ONJ progressed in 3 patients (Cases 8, 10 and 11) after 3, 4 and 11 months discontinuation of denosumab respectively.

All patients in this series were conservatively managed with 0.12% chlorhexidine gluconate rinses 2 to 3 times per day. The use of surgical modalities in addition with bone fluorescence to aid visualization in the intra-operative delineation of the necrotic bone has yielded great result (Otto et al., 2013; Ristow et al., 2015). Surgical techniques were not employed in the management of the patients in our series.

Corticosteroids, active tobacco use and comorbidities such as a medical history of diabetes mellitus or rheumatoid arthritis have been associated with an increased risk for ONJ (Saad et al., 2012; Kyrgidis et al., 2008). Tobacco use has been inconsistently reported as a risk factor for ONJ. In one case-control study, tobacco was found to be a risk factor for ONJ in cancer patients while in another case-controlled study, tobacco use was not associated with ONJ in cancer patients (Kyrgidis et al., 2008; Tsao et al., 2013). Genetic background may increase risk for ONJ; series from Greece and Turkey have demonstrated relatively higher rates of ONJ than have been reported elsewhere (Nicoletti et al., 2012; Lehrer et al., 2009; Sarasquete et al., 2008; Hoff et al., 2011; Zervas et al., 2006; Dimopoulos et al., 2006; Cetiner et al., 2009). 92.3% of the patients in our cohort were of Caucasian descent of unspecified countries.

For osteoporotic patients: The American Dental Association Council on Scientific Affairs has stated that patients on low cumulative doses (<2 years) of bisphosphonate or denosumab can undergo invasive dental procedures without discontinuation of antiresorptive therapy (Hellstein et al., 2011). Also, The International Task Force on ONJ recommends discontinuation of bisphosphonate in patients with cumulative doses (>4 years) (Ruggiero et al., 2014). In contrast, in our series, 5 of the 7 oncologic patients who had dental extractions as the precipitating event received less than two years' cumulative doses of denosumab (range: 6 – 22 months). Also, patients developed ONJ at a cumulative dose far less than 4 years (range: 5 – 36 months), with one patient developing ONJ after the fifth dose, 5 months after her initial dose.

Invasive surgical dental procedures such as dental extraction, periodontal surgery, or implant placement are considered the major risk/precipitating factor for the development of ONJ with 51–61% of patients having a surgical procedure in their history that may be considered either a risk or precipitating factor (Fehm et al., 2009; Vahtsevanos et al., 2009; Saad et al., 2012; Watters et al., 2013). Similarly, in this series the ONJ lesions in 7 of 13 (54%) patients were related to dental extraction; the rest were determined to be spontaneous in origin.

Conclusion

We present our experience with denosumab-related ONJ from a single institution. This series should contribute to the existing sparse clinical literature on this topic. The pathogenesis, treatment and outcome of ONJ are complex and multifactorial. Patients treated with denosumab may be more prone to developing ONJ even without precipitating dental event. ONJ may develop earlier in patients receiving denosumab and the role of drug discontinuation prior to an invasive dental procedure or after the onset of ONJ still remains debatable. The number of patients in this series is inadequate to draw any definitive conclusion or comparison, and further retrospective analyses as well as prospective studies of the effectiveness of denosumab holidays for ONJ prevention are indicated. Prevention of ONJ still remains the most important goal, and this is most directly accomplished by avoiding invasive dental procedures.

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Figure 1.
Clinical pictures of exposed necrotic bone in patients with denosumab-related osteonecrosis of the jaw (Cases 1 (A), 2 (B), 5 (C) and 11(D))

Figure 2.
Clinical pictures of exposed necrotic bone at initial presentation (A) and at 8 months following discontinuation of denosumab with complete mucosal coverage after exfoliation of the necrotic bone (B), Case 4

Figure 3. Clinical pictures of exposed necrotic bone at initial presentation (A) and at 3 months following discontinuation of denosumab; an increase in the size of the exposed bone (B), Case 8

Table 1

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

Table 2

Case No.	ONJ location	Size of ONJ at first clinical presentation (mm)	ONJ risk factor	Stage of ONJ at initial presentation	Time from dental extraction to the onset of ONJ (months)	Number of Denosumab dose at the onset of ONJ	Denosumab discontinued (Yes / No)	Duration of drug holiday after ONJ (months)	Follow-up duration (months)	Outcome / Size of ONJ at last follow-up (mm)
1	Maxilla	3 × 2	Extraction #10	2	6	6	Yes	15	26	Resolved
2	Mandible	2 × 2	Extraction #30	1	Non-completely mucosalized extraction socket	30	Yes	3	2	Partial resolution / 1 × 1
3	Maxilla	3	Spontaneous	2	-	5	No	-	-	-
4	Mandible	7 × 6	Spontaneous	1	-	8	Yes	8	6	Resolved
5	Mandible	5	Extraction #19	2	7	7	No	-	24	Progressed / 6 × 3
6	Maxilla	7 × 4	Spontaneous	2	-	28	Yes	7	2	Resolved
7	Mandible	1 × 1	Extraction #21	1	4	6	Yes	16	1	No changes
8	Mandible	6 × 5	Extraction #19 and 20	2	4	22	Yes	3	2	Progressed / 10 × 7
9	Mandible	12 × 4	Spontaneous	1	-	7	No	-	-	DOD a month later
10	Mandible	1 × 1	Spontaneous	1	-	29	Yes	4	3	Progressed / 5
11	Mandible	2 × 1	Spontaneous	1	-	6	Yes	11	21	Progressed / 10 × 5
12	Mandible	1 × 1	Extraction #31	1	12	36	Yes	2	1	No changes
13	Mandible and Maxilla	Mandible – 50 Maxilla – 8	Extraction #14, 15, 16, 17, 18, 19	2	12	8	Yes	2	-	-