



DENOSUMAB-RELATED OSTEONECROSIS OF THE JAWS: A CASE REPORT

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ABSTRACT

Bisphosphonates are potent and effective drugs frequently used to prevent the skeletal complications associated with postmenopausal osteoporosis in women, to manage patients with multiple myeloma, hypercalcemia, and metastasis of cancer to the bone.

The search for new medications with the same therapeutic effectiveness as the bisphosphonates but fewer side effects has resulted in the discovery of Denosumab, a human monoclonal antibody against the receptor activator for nuclear factor kappa B ligand (RANKL), therefore inhibiting osteoclast differentiation and function. Denosumab is a class of drugs that are entirely different from the traditional antiresorptive drugs, the bisphosphonates. Denosumab has several advantages, including better tolerability, ease of subcutaneous injection, a shorter half-life, and a reduced incidence of nephrotoxicity.

Patients receiving bisphosphonates are at risk to develop a severe devastating complication - osteonecrosis of the jaws (ONJ) - which is challenging to treat.

Since 2010 there have been reports of ONJ in patients taking denosumab.

In the 2014 position paper of the American Association of Oral and Maxillofacial Surgeons, the nomenclature "bisphosphonate-related osteonecrosis of the jaw" was changed to "medication related osteonecrosis of the jaw" (MRONJ). The change is justified to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies.

Here we report a development of denosumab-related osteonecrosis of the jaw (DRONJ) - a new type of bony necrosis- in patient with bone metastases of breast cancer on Denosumab therapy. The patient has no previous history of taking bisphosphonates.

Keywords: Denosumab, osteonecrosis, Denosumab-related osteonecrosis of the jaws

INTRODUCTION

Bisphosphonates are widely used potent and effective anti-resorptive agents for the treatment of diseases in which there is an increase in osteoclastic resorption, including malignancy-associated hypercalcemia, post-

menopausal osteoporosis, osteopenia, Paget's disease, multiple myeloma, and metastasis of cancer to the bone.

In most solid tumors, bones are one of the most common locations for metastasis, along with the liver and lungs. [1] Bone metastases occur in approximately 70% of patients with metastatic disease. [2] The location of bone metastases partly affects the patient's symptomatology, quality of life and prognosis. Although bone metastases can occur in any patient with advanced stage cancer, some tumors have a higher risk, including breast, prostate, lung, kidney and thyroid cancers, among others.[1]

To date, bisphosphonate has been widely used as an antiosteoclastic and antineoplastic agent.[2]

The search for medications with the same therapeutic effectiveness as the bisphosphonates but fewer side effects has resulted in the discovery of denosumab, a human monoclonal antibody that inhibits osteoclasts. [3]

Denosumab is in a class of drugs that are entirely different from the traditional antiresorptive drugs, the bisphosphonates. Denosumab suppresses osteoclast formation by targeting preosteoclasts in the extracellular environment, whereas bisphosphonates target mature osteoclasts and inhibit bone resorption through intracellular effects. [2]

Here we report a development of denosumab-related osteonecrosis of the jaw (DRONJ) - a new type of bony necrosis- in patient with bone metastases of breast cancer on Denosumab therapy. The patient has no previous history of taking bisphosphonates.

CASE REPORT

We report a development of denosumab-related osteonecrosis of the jaw (DRONJ) - a new type of bony necrosis- in 71-years old female with bone metastases of breast cancer on Denosumab therapy since 2013. The patient has no previous history of taking BPs and no history of radiation.

The patient presented in our office with exposed necrotic bone on the lingual aspect of the right side of the mandible, in the region of the missing tooth 46. The necrotic bone area ranged about 20mm and was associated with no inflammation- no erythema, edema or suppuration was found. (Fig. 1)

Fig. 1. Exposed necrotic bone on the lingual aspect of the right side of the mandible, in the region of the missing tooth 46.



After taking a detailed history the patient reported that the extraction of tooth 46 was realized during the treatment with Denosumab. The osteonecrosis developed after the 13th application of the drug on the site of extraction of tooth 46. On Fig. 2 is presented the X-ray taken on the time of the clinically evident osteonecrosis.

Fig. 2- An X-ray taken on the time of the clinically evident osteonecrosis



Patient was managed conservatively with 0.12% chlorhexidine gluconate rinses 2 to 3 times per day. The patient should be monitor closely because of the progressive nature of the medication-related osteonecrosis of the jaws.

DISCUSSION

Denosumab is a human monoclonal immunoglobulin 2G (Ig2G) antibody. It functions to decrease bone metabolism by inhibiting a critical step in the differentiation of osteoclasts. Specifically, denosumab inhibits the binding of receptor activator of nuclear factor-kappa B ligand (RANKL) in the cell membrane of osteoblasts to its constituent receptor activator of nuclear factor- kappa B- (RANK) in the cell membranes of osteoclasts and osteoclast precursor cells. RANK and RANKL are critical in triggering the cellular pathway that leads to upregulation of bone metabolism. [3]

Bone metastases are characterized by increased bone turnover and altered balance between osteogenesis and osteolysis, with activation of the RANK and its ligand (RANKL). Thus, since it has an anti-RANKL mechanism of action, denosumab ultimately reduces bone resorption caused by metastatic lesions. [1]

Early clinical trials have demonstrated that this new drug is well tolerated and that its use results in a sustained reduction in bone turnover and an increase in bone mineral density. [2]

Denosumab has several advantages over bisphosphonates, including better tolerability, ease of subcutaneous injection, a shorter half-life, and a reduced incidence of nephrotoxicity, rendering it the drug of choice for patients with renal diseases or for those with diseases with a propensity toward renal dysfunction, such as renal cell cancer and prostate cancer. [2]

The FDA approved XGEVA® (Denosumab) in November 2010 as a subcutaneous injection 120 mg every 4 weeks for the prevention of skeletal related events in patients with bone metastases from solid tumors.

Patients receiving bisphosphonates are at risk to develop a severe devastating complication - osteonecrosis of the jaws (ONJ) - which is challenging to treat and can lead to oncologic treatment interruptions as well as diminished quality of life. [4]

Although most of the reported cases of osteonecrosis of the jaw (ONJ) are associated with bisphosphonates, since 2010, ONJ cases have also been described in patients taking denosumab. Therefore, in the 2014 position paper of the American Association of Oral and Maxillofacial Surgeons, the nomenclature “bisphosphonate-related osteonecrosis of the jaw” was changed to “medication related osteonecrosis of the jaw” (MRONJ). The change is justified to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies. [5]

MRONJ is defined as ONJ in patients with current or previous treatment with antiresorptive or antiangiogenic agents and no history of radiation therapy or obvious metastatic disease to the jaws who have exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks. [2, 5]

Osteonecrosis of the jaw as a result of treatment with denosumab is a new type of bony necrosis, the exact pathogenesis of which is not fully clarified. [6]

The incidence of denosumab-related ONJ was reported to be approximately 0.01% to 0.03% in patients with osteoporosis and 1% to 2% in patients with cancer, rates that appear similar to that associated with bisphosphonates. [2, 5]

A study showed that among cancer patients exposed to zoledronate or denosumab, the incidence of developing ONJ was, respectively, 0.6 and 0.5% at 1 year, 0.9 and 1.1% at 2 years and 1.3 and 1.1% at 3 years with the risk for ONJ among denosumab-exposed subjects plateauing between years 2 and 3. [5]

It appears that the risk for ONJ among cancer patient exposed to denosumab is comparable to the risk of ONJ in patients exposed to BPs. [4, 5, 7, 8]

Although bisphosphonate-induced ONJ has been reported to occur after a mean administration duration of 39.3 months and 35 infusions in oncology patients, it is interesting that all published cases of denosumab-related ONJ occurred early after commencement of therapy, independent of the number of previous administrations. [2]

The risk factors for developing DONJ or BRONJ are similar. These include the potency of the antiresorptive medication, a longer duration leading to an increased cumulative dose, age over 60 years, preexisting oral infection, previous dental treatment, chemotherapy, regular steroid use and smoking. Local risk factors include dental extractions, oral, periodontal and periapical surgeries, local anatomical considerations and dental implant placement. [5, 8]

One advantage that denosumab has over bisphosphonates in terms of drug discontinuation is that denosumab has a much shorter half-life (25.4 days) compared to bisphosphonates (10-12 years). [2] Saad et al. found that patients taking denosumab had a more rapid resolution of ONJ than patients taking the bisphosphonate zoledronate. They suggested that the more rapid recovery may be related to the “reversible” inhibition of RANKL. [2, 3] RANK ligand inhibitors do not bind to bone and their effects on bone remodeling are mostly diminished within 6 months of treatment cessation. [5]

It has been reported that the cessation of osteoclast activity occurs within 6 hours of subcutaneous denosumab injection and returns to normal function approximately 6 months thereafter. [2, 5]

The concept of a drug holiday in patients receiving denosumab is controversial and there are no studies to support or refute the strategy of stopping denosumab therapy in the prevention or treatment of MRONJ; how-

ever, it is possible that cessation of denosumab therapy could reduce the risk of ONJ and allow the restoration of bone remodeling. Otto et al. recommended that any surgical intervention for ONJ be withheld for at least 4 months after denosumab administration to avoid manifestation of ONJ. However, there is currently no specific protocol for a drug holiday from denosumab, and further study is needed to develop an appropriate strategy. [2, 5]

There are no universally accepted treatment protocols for ONJ, and strategies range from conservative nonsurgical (including chlorhexidine rinses, systemic antibiotics, and pain medications) therapy to early surgical intervention. If osteonecrosis develops, nonsurgical management based on antibiotic therapy with a “drug holiday” may be beneficial. [2, 4] If the areas of exposed mandibular bone are traumatizing adjacent soft tissues, an alveolectomy is warranted. Disruption of thin surrounding mucosa should be avoided to prevent further progression of the necrosis. Similarly, if an area of bone sequestrum is evident on X-ray and can be removed without disruption of surrounding soft tissue, it should be removed and primarily closed if possible. [4, 5]

Unlike osteoradionecrosis, hyperbaric oxygen therapy does not appear to provide benefit. [4, 5]

CONCLUSION

With the approval of denosumab for treatment of osteoporosis and bone metastasis of cancer, the oral health-care providers must be vigilant of the possibility that a new type of bone necrosis (DRONJ) can develop in patients receiving denosumab.

Evaluation of a case of ONJ developing in a patient receiving denosumab and review of the pharmacokinetics of denosumab suggest that denosumab is more beneficial than the bisphosphonates in the management of ONJ.

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