**CLINICAL VIGNETTE**

# A Case of Osteonecrosis of the Jaw after Treatment with Denosumab

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***Case Report***

A 63-year-old woman underwent a left mastectomy for a 3 cm invasive lobular carcinoma of the upper breast with 1 of 26 positive axillary lymph nodes for a stage IIB T2N1M0 breast cancer, which was estrogen receptor (ER) positive, progesterone receptor (PR) positive, and HER-2 negative. After surgery, she received chemotherapy with doxorubicin and cyclophosphamide for 4 cycles, followed by 4 cycles of docetaxel chemotherapy. Endocrine therapy with anastrozole was initiated after the completion of chemotherapy.

After less than 4 years of adjuvant anastrozole therapy, she developed pain in her pelvis and imaging revealed bony metastases in the sacrum, lumbar spine, and thoracic spine. Biopsy of the sacrum demonstrated metastatic breast cancer, ER positive, PR positive, and HER-2 negative.

First-line treatment for her metastatic breast cancer to bone consisted of fulvestrant with denosumab. Her disease stabilized with the fulvestrant therapy for 9 months at which point she then progressed in the bone. She lived another 3 years and was treated for her metastatic breast cancer with a variety of endocrine agents; she ultimately died from a cardiac event.

The denosumab therapy was initiated for her metastatic breast cancer to bone. She was treated with monthly denosumab for 15 months at which point she developed osteonecrosis of the jaw (ONJ) and denosumab was discontinued. She then was evaluated by a number of dentists and oral surgeons, treated with a variety of antibiotics, and ultimately had her tooth extracted with delayed healing.

***Discussion***

Bone metastases from solid tumors can significantly decrease a patient's quality of life, causing pain and neurologic complications, which can require therapeutic interventions such as surgery or radiation therapy. Bisphosphonates were the initial bone targeted therapies evaluated in individuals with advanced cancer with bony metastases. Studies revealed that bisphosphonates did decrease skeletal-related events, defined as fracture, need for radiation therapy to bone, surgery to bone, or spinal cord compression.[1]

Denosumab, a monoclonal antibody that functions as a RANKL inhibitor, is used not only to treat osteoporosis and drug-induced bone loss but also decreases skeletal-related events from bone metastases due to solid tumors. When evaluated in a meta-analysis, denosumab was found to be more effective at decreasing such skeletal complications when compared to the intravenous bisphosphonates zoledronic acid and pamidronate.[2]

In addition, a metanalysis of trials of adjuvant zoledronic acid in women with early breast cancer[3] revealed that adjuvant bisphosphonates reduce the rate of metastatic breast cancer to bone (1.2% absolute benefit at 10 years) and improve breast cancer survival in postmenopausal women (1.8% absolute benefit at 10 years). The absolute benefit is small but significant and has led to the increased use of adjuvant bisphosphates in the treatment of postmenopausal women. A subsequent study revealed a similar improvement in disease free survival when denosumab was administered adjuvantly to postmenopausal women with a 3% improvement in disease free survival for all women on the study and an even larger 10.5% improvement for women with tumors larger than 2 cm.[4]

These data have led to an increased use of denosumab and parenteral bisphosphonates in the adjuvant treatment of non-metastatic breast cancer, in addition to their use in the setting of skeletal metastases. Yet, such treatment comes at both financial and medical costs with an increase in toxicities, including the risk of ONJ. When administered to prevent skeletal complications from metastatic breast cancer, these agents are often given monthly, which is a much higher dose intensity than when given for other indications, resulting in a higher risk of ONJ.

Medication related ONJ is defined as exposed bone or bone that can be probed through a fistula in the maxillofacial region that has persisted for more than 8 weeks in an individual with current or previous treatment with antiresorptive or antiangiogenic agents, no history of radiation therapy to the site, and no obvious metastatic disease in the jawbones. Patients may present with exposed and necrotic bone that can remain asymptomatic for prolonged periods of time, even years. Soft tissue inflammation can lead to symptoms, and local tooth, jaw, or gingival symptoms may precede the exposure of bone. Such symptoms may occur spontaneously or at the site of dentoalveolar extraction. Dentral extraction precedes the development of ONJ in about 2/3 of the cases.

Although oral bisphosphonates have been associated with ONJ, the risk is higher with IV bisphosphonates and is most common in patients receiving monthly IV therapy. The incidence increases with longer duration of therapy, particularly after 4 years. One study[5] revealed an incidence of 1.1% in the first year

and 4.1% in subsequent years of treatment. A slightly higher incidence is seen with denosumab than with zoledronic acid. Although ONJ can occur without a precipitating event, tooth extraction, dental fractures, poorly fitting dentures, and periodontal disease are some of the other underlying oral conditions that can precede ONJ in the setting of antiresorptive agents.

In order to minimize the risk of ONJ, patients should have a complete dental evaluation before the start of therapy with treatment of infections, dental extractions, or other necessary procedures being completed before the initiation of the antiresorptive agents. While on treatment with these medications, patients should maintain good oral hygiene and routine dental evaluations, as well as avoid invasive dental procedures, if possible. For patients who do need dental work, it is recommended to hold antiresorptive treatment for 2-3 months before such therapy, although there are little data to suggest an optimal interval for holding these medications to decrease the risk of ONJ.

Long-term studies do not exist for the treatment of medication related ONJ. The goal of management is to control pain, control infection, and minimize progression of necrosis. Conservative management with oral rinses and/or antibiotics in general is the first treatment approach with resection reserved for ONJ that does not heal with non-surgical intervention.

Although ONJ can significantly decline the quality of life for an individual who develops this complication, the benefit of preventing skeletal-related events statistically outweighs this risk for most patients with metastatic malignancies for whom such denosumab or bisphosphonate therapy is considered. Newer schedules of less dose intense denosumab and bisphosphonate therapy given every 3 months might offer adequate protection against skeletal events while decreasing the risk of ONJ.

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