Clinical Update: A Nonhealing Fractured Mandible

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J.C. is a 70-year-old female who was diagnosed in 1990 with stage I breast cancer. The primary tumor was 8 mm in maximum diameter with negative nodes. The breast cancer profile revealed that the tumor was estrogen receptor-positive and progesterone receptor-negative. No adjuvant treatment was recommended at the time. In 1998, J.C. presented with left shoulder pain, an inability to extend her left arm, and occasional right hip pain. A bone scan revealed increased uptake in the right superior pubic ramus that was suspicious for metastatic disease as well as increased uptake in the left shoulder. A magnetic resonance imaging (MRI) scan of the left shoulder revealed an 8 x 5 x 5 cm mass involving the superior aspect of the scapula. A computed tomography- (CT-) guided needle biopsy of the scapula mass showed poorly differentiated non-small cell carcinoma that was consistent with her primary breast disease. The scapula mass was estrogen receptor-positive, progesterone receptor-positive, HER2/neu 3+, and fluorescence in situ hybridization-negative. All other staging examinations were negative. J.C. has a history of hypertension and type II diabetes mellitus, which are well controlled.

J.C. was enrolled in a clinical trial comparing letrozole with tamoxifen and underwent radiation to the scapula and right hip. She also was started on pamidronate for bone metastasis. J.C. initially had a positive response to therapy; however, she was diagnosed with progressive bone disease in 2001. She was removed from the study and, after unblinding, was found to have been on the letrozole arm. After undergoing radiation to the scapula and under going pamidronate therapy, J.C. was again found to have progressive bone and liver disease, and her hormonal therapy was discontinued. She was started on docetaxel with ongoing zoledronic acid therapy.

Unfortunately, J.C. was found to have a dental abscess and underwent tooth extraction with a subsequent fracture of her left maxilla. Open reduction and internal fixation were performed, but after two months the fracture had not healed and J.C. was experiencing significant pain. Her chemotherapy treatments frequently were delayed. Differential diagnosis for the left maxilla may include metastatic breast cancer, poor wound healing related to immunosuppression secondary to chemotherapy, poor wound healing related to diabetes mellitus, or osteonecrosis of the jaw.

In June 2003, J.C. was referred to an oral surgeon at a major teaching institution. The diagnosis by the oral surgeon was osteonecrosis of the jaw secondary to bisphosphonate therapy, which was discontinued. She was treated with multiple antibiotic therapies and hyperbaric oxygen treatments, but her symptoms and wound healing did not improve. Surgery was not an option because of the avascular necrosis involvement in the mandible and the potential for further open wounds and poor wound healing postoperatively (see Figure 1).

In July 2003, J.C. underwent restaging examinations and was found to have progressive liver metastasis. She was given cyclophosphamide, doxorubicin, and fluorouracil until her disease progressed again in November 2003. Since then, she has been treated with capecitabine and zoledronic acid, with dramatic improvement in the liver metastasis and no further bony progression. Currently, J.C. feels well from the standpoint of her breast cancer and therapy, but her left maxillary area remains open, draining, and painful.

Definition

Osteonecrosis, or avascular necrosis, results from temporary or permanent loss of blood supply to the bones. The condition can be caused by trauma or damage to the blood vessels that supply blood to the bones, blockage by air or fat embolisms, hypercoagulable states, or vasculitis. A loss of blood supply causes minute bone fractures, with ultimate bone collapse. Osteonecrosis of the jaw is similar to “phossy jaw,” which dates back to 1845 and was found in employees in match factories that used white phosphorus in manufacturing. Phossy jaw reportedly was painful,

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disfiguring, and refractory to treatment (Maxillofacial Center for Diagnostics and Research, 2005).

**Bone Physiology and Bisphosphonate Mechanism of Action**

Normal bone remodeling consists of osteoclastic activity that promotes bone resorption and osteoblastic activity that promotes bone growth. Bisphosphonates obstruct bone resorption through selective concentration at the border of the active osteoclast and the bone resorption surface, resulting in the inhibition of osteoclastic activity. In bone disorders with increased osteoclastic activity, such as osteoporosis, multiple myeloma, hypercalcemia of malignancy, and bone metastases, bisphosphonates have been found to be beneficial in preventing skeletal fractures and reducing bone pain and bony complications (Carter, Goss, & Doecke, 2005; Viale & Sanchez Yamamoto, 2003). The exact mechanism is unknown, but researchers have suggested that decreased osteoclastic activity may occur as a result of inhibition of osteoclast development from precursor cells, an increase in osteoclast apoptosis, stimulation of osteoclast inhibitory factor, or reduction of osteoclast activity (Carter et al.).

Osteoclasts are critical in the maintenance of bone viability. Osteocytes have a life span of approximately 150 days. Osteoclasts then resorb the mineral bone matrix and release bone morphogenetic protein, which induces stem cell differentiation into osteoblasts and the formation of new bone. When osteoclastic function is reduced, dead osteocytes are not replaced, the bone capillary network is not maintained, and avascular bone necrosis may occur (Carter et al., 2005). Other suggested pharmacologic properties of bisphosphonates that may play a role in osteonecrosis are the inhibition of tumor cell proliferation and the inhibition of angiogenesis (Melo & Obeid, 2005).

**Incidence and Risk Factors**

The exact incidence of osteonecrosis in patients with cancer is unknown (Novartis Pharmaceuticals Corporation, 2005). The risk factors for osteonecrosis include trauma, female gender, advanced age, edentulous regions, combination cancer treatment with chemotherapy, radiation therapy or steroid therapy, blood dyscrasias, metastatic disease, anemia, coagulopathy, surgical dental procedures, alcohol or tobacco use, and previous infection. Studies suggest that approximately 80% of patients with osteonecrosis of the jaw have undergone dental extraction (Marx, 2003). Patients who have been receiving bisphosphonates for more than six months are at the highest risk (Ruggiero, Mehrotra, Rosenberg, & Engroff, 2004). In addition, osteonecrosis of the jaw occurs predominantly in patients receiving the more potent nitrogen-containing bisphosphonates, pamidronate and zoledronate, rather than the less potent bisphosphonate, alendronate.

**Clinical Presentation**

The initial symptoms of osteonecrosis of the jaw include joint stiffness, limited motion, muscle spasms, and pain. In a majority of patients, the pain is neuralgic in nature, slowly progressing from tenderness to severe pain, and may be located in several regions of the maxilla or mandible. If dental extraction occurs, bone healing may be compromised and secondary infection may occur (Melo & Obeid, 2005). Diagnosis of osteonecrosis is based on clinical findings and imaging studies, such as plain films and MRI, as well as panoramic imaging to rule out other etiologies (Novartis Pharmaceuticals Corporation, 2005). “Biopsy should be performed only if metastasis to the jaw is suspected” (Novartis Pharmaceuticals Corporation, p. 5).

**Treatment**

Currently, a lack of effective treatments exists for osteonecrosis of the jaw (Carter et al., 2005). Preventive measures are critical and include the following (Novartis Pharmaceuticals Corporation, 2005).

- Patients should undergo dental examination before the initiation of IV bisphosphonate therapy.
- Patients should have routine dental examinations that may include panoramic jaw radiography.
- Patients may undergo routine dental cleaning if soft-tissue injury is avoided.
- Prophylactic antibiotics are not recommended before routine dental examinations unless otherwise required for prophylaxis of bacteremia in patients at risk.
- Root canal therapy is preferred over dental extraction to manage dental infections.
- Patients must be educated “regarding the importance of good dental hygiene and symptom reporting” (p. 4).
- Patients must be educated regarding the proper fit of dentures and remove them at night.
- Patients receiving bisphosphonates should receive ongoing reminders about the importance of notifying their oncologists before undergoing any dental procedures.
- Patients should be referred to an oral surgeon immediately if symptoms occur.
- A brief visual inspection of the oral cavity should be conducted at baseline bisphosphonate therapy and at every follow-up visit by a healthcare provider.
- Hyperbaric oxygen treatments have not been shown to be effective and therefore are not recommended.
- Intermittent or continuous antibiotic therapy may be administered to prevent secondary infections and reduce pain. Wound cultures may be helpful to identify appropriate antimicrobial agents. Several antibiotic, antifungal, and antiviral agents have been found to be useful in treating osteonecrosis (see Figure 2).

**Summary**

Bisphosphonates have shown significant clinical benefit in reducing skeletal fractures in patients with multiple myeloma or bone...
metastases from solid tumors (Novartis Pharmaceuticals Corporation, 2005). However, further research is needed to investigate bisphosphonate therapy and osteonecrosis of the jaw. A definite causal relationship between bisphosphonate therapy and osteonecrosis of the jaw has not been established; therefore, each patient must be evaluated individually to determine the risks and benefits of continuing bisphosphonate therapy. Research has included retrospective studies, small samples, and case reports as described previously (Viale & Lin, 2005). Whether discontinuing bisphosphonates would alter the risk of developing osteonecrosis of the jaw is not clear; therefore, no recommendations have been developed. One study suggested that the pharmacokinetic properties of bisphosphonates may persist for as long as 12 years once bone uptake has occurred, suggesting the possibility of an increased risk of developing osteonecrosis of the jaw for several years after discontinuation of the drug (Lin, Russell, & Gertz, 1999). Until further research has been conducted, the best strategies are prevention and education.

Unfortunately, J.C.’s dental extraction occurred before the current increased awareness, information, and literature regarding osteonecrosis of the jaw. Oncology nurses must be knowledgeable about osteonecrosis of the jaw and conduct ongoing assessment of patients receiving bisphosphonate therapy. Oncology nurses also play a key role in educating patients about preventive strategies and instructing them to report immediately to a healthcare provider if symptoms occur.

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