The treatment of bisphosphonate–associated osteonecrosis of the jaws with bone resection and autologous platelet-derived growth factors

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Bisphosphonates are used widely in the treatment of osteoporosis, metastatic cancer in bone, hypercalcemia associated with malignant disease and multiple myeloma. A limited number of patients receive bisphosphonates intravenously to treat multiple myeloma and metastatic carcinoma in bone; many more patients receive such oral bisphosphonates as alendronate and risedronate to manage their osteoporosis. In 2003, more than 20 million prescriptions were written for oral bisphosphonates.[1]

A new oral complication of cancer therapy has been identified: bisphosphonate-associated osteonecrosis (BON). Reports have documented avascular necrosis of the jaws associated with the use of bisphosphonates, especially when they are administered intravenously.[2,3] Bisphosphonates are associated with poor healing after dental extractions, spontaneous intraoral ulceration, and bone necrosis of the maxilla and mandible. This new clinical entity has gained increased attention since 2003,[2] with new cases reported daily.

Since the publication of the initial reports, we have managed the care of a cluster of patients who

ABSTRACT

Background. Bisphosphonates administered intravenously are used to treat patients with cancer who have hypercalcemia associated with malignant disease, multiple myeloma or metastatic tumors (breast, lung, prostate) in the bones. Bisphosphonates are bone resorption inhibitors and have been associated with osteonecrosis of the jaws. In this article, the authors provide an alternative treatment modality for refractory bisphosphonate-associated osteonecrosis (BON).

Case Description. The authors treated 12 patients with refractory BON and a history of long-term bisphosphonate therapy. Each patient had mucosal ulceration with exposed necrotic bone. The treatment combined bone resection with platelet-derived growth factors (PDGFs). The surgical intervention they used was a marginal resection limited to the alveolar bone. Ten of the patients recovered with complete mucosal and bone healing.

Conclusion. BON has been shown to be refractory to antibiotics, minor local débridement and 0.12 percent chlorhexidine oral rinse. Treatment of refractory BON with a combination of marginal resection and PDGF has shown favorable results, including complete wound healing in most patients. This modality has been shown to be effective in treating BON and may be a useful alternative to existing treatment strategies.

Key Words. Bisphosphonates; bisphosphonate-associated osteonecrosis; platelet-derived growth factors; platelet-rich plasma; marginal bone resection; bone healing; mucosal healing.

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have BON. The oral lesions resulting from BON are similar in appearance to those of osteoradionecrosis. BON, however, has a different pathophysiology and, therefore, does not respond to hyperbaric oxygen. The intraoral lesions manifest as mucosal ulcerations with dehiscence of soft tissue, exposing the underlying necrotic bone. The lesions often are painful and persistent, and they do not respond to conventional surgical débridement. The treatment of BON is controversial because there are many different treatment guidelines and philosophies. Dentistry is starting to work toward the goal of having one acceptable management guideline. Treatments that enhance wound healing by using growth factors are being considered.

In this article, we report our experience in managing the treatment of 12 patients with refractory osteonecrosis of the jaw associated with long-term bisphosphonate use. We treated the patients with marginal resection, platelet-derived growth factors (PDGFs) and a resorbable membrane. Of the 12 patients treated with this protocol, 10 experienced complete mucosal and bone healing. This report proposes an alternative treatment for patients with BON.

PATIENTS AND METHODS

Between August 2004 and December 2006, 12 patients' general dentists referred them to us for treatment of exposed bone in the maxilla and mandible that was associated with bisphosphonate use. Four of the patients were male, and eight of the patients were female (age range, 43-83 years). Three patients were treated at Faxton-St. Luke's Healthcare Dental Services, New Hartford, N.Y., and nine patients were treated in a private office. All of the patients had received diagnoses of and been treated for malignant disease at Faxton-St. Luke's Regional Cancer Center, Utica, N.Y., and they all had bone scans showing malignant disease in the bone outside of their jaws. Three patients had multiple myeloma, one patient had prostate cancer, and eight patients had breast cancer. Two patients had a history of cigarette smoking. All of the patients underwent panoramic radiographic evaluation before surgical débridement. After surgery, we followed each patient every two to four weeks and took a panoramic radiograph at six months. The histopathologic results for all of the patients revealed only osteonecrosis and never any bone malignancy.

Initially, we managed the patients' treatment conservatively. Treatment included local minor bone débridement, 0.12 percent chlorhexidine oral rinse, and long-term or intermittent antibiotics for a minimum of six months. We interrupted all of the patients' bisphosphonate therapy after consulting with their oncologists at Faxton-St. Luke's Regional Cancer Center. Each patient had mucosal ulceration and exposed necrotic bone (Figure 1). The original sizes of the necrotic bone defects ranged from 5 to 25 mm. In all of the patients, we limited surgical intervention to a marginal resection within the alveolar bone. We based this intervention on our clinical findings during surgery, as well as radiographic evaluation of the jaws. The marginal resection included the necrotic bone segment of the jaw, leaving behind healthy appearing bone. After we completed the resection, we applied platelet-rich plasma (PRP) topically over the bone defect as an adjunctive therapy. We then placed a resorbable collagen membrane (Ossix Plus, ColBar LifeScience, Herzliya, Israel) impregnated with PRP over the bony cavity.

The wound was closed primarily in eight of the 12 patients. In the other four patients, the wound healed by means of secondary intention over the resorbable membrane. We gave each patient 300 milligrams of clindamycin four times a day for 10 days and then prescribed a maintenance dose of 300 mg twice a day. All patients were instructed to use 0.12 percent chlorhexidine oral rinse twice a day. Ten patients achieved complete bone and mucosal healing after six months. One of the two remaining patients initially experienced wound closure, but wound dehiscence occurred postoperatively. The second patient never experienced full mucosal and bone healing by means of secondary intention over the resorbable membrane. These two patients' original defects improved mildly even though complete bone and mucosal healing was not achieved. Both patients reported an improvement in symptoms and pain.

PRP preparation. During surgery, we obtained 20 milliliters of autologous blood for each patient. We separated the 20 mL of blood into two 10-mL collection tubes and placed them in an automated tabletop centrifuge (model no.

ABBREVIATION KEY. BON: Bisphosphonate-associated osteonecrosis. **PDGFs:** Platelet-derived growth factors. **PPP:** Platelet-poor plasma. **PRP:** Platelet-rich plasma.