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

Michael C. Adornato, DDS; Iyad Morcos, DMD; James Rozanski, DDS

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.

CS6C, Vulcun Technologies, Grandview, Mo.) in which it was spun for 11 minutes to separate it into red blood cells, platelet-poor plasma (PPP) and PRP. We removed the yellow PPP layer at the top of each collection tube so we could access the middle layer of PRP, which we removed from each collection tube. It takes 10 mL of whole blood in each collection tube to produce 1 mL of PRP. We prepared 2 mL of PRP for each patient. We then resuspended topical thrombin with 5 mL of calcium chloride. We mixed 0.2 mL of this solution with the PRP for proper activation of the growth factors and clotting cascade. We applied the resulting PRP gel to the bone cavity and the resorbable collagen membrane. This gel forms a fibrin network with cancellous cellular marrow and facilitates epithelial growth along the resorbable membrane.

Results of bisphosphonate therapy. Eight patients (67 percent) received 4 mg of zoledronate intravenously every three to four weeks, and four patients (33 percent) received 90 mg of pamidronate intravenously every three to four weeks (Table). They all received bisphosphonate therapy for at least one year.

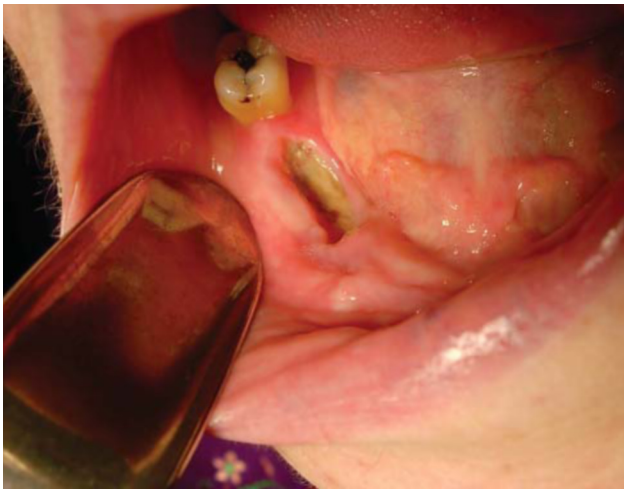

Figure 1. Exposed necrotic bone in the mandible and mucosal ulceration related to zoledronate therapy.

Eight patients (67 percent) had asymptomatic exposed bone that was identified by us and the patients' dentists during routine dental examinations, and four patients (33 percent) had an area of exposed bone and pain. Three patients

TABLE

Clinical characteristics of patients with osteonecrosis of the jaws.

PATIENT	AGE (YEARS)	SEX	MALIGNANT DISEASE	TYPE OF BISPHOSPHONATE THERAPY	SITE	HISTOPATHOLOGY
1	59	M	Breast cancer	Zoledronate	Mandible	Chronic osteomyelitis
2	66	F	Breast cancer	Zoledronate	Mandible	Chronic osteomyelitis
3	73	M	Multiple myeloma	Pamidronate	Maxilla	Chronic osteomyelitis
4	73	F	Breast cancer	Pamidronate	Maxilla	Chronic osteomyelitis
5	75	F	Multiple myeloma	Zoledronate	Mandible	Chronic osteomyelitis
6	62	F	Breast cancer	Zoledronate	Mandible	Chronic osteomyelitis
7	51	M	Multiple myeloma	Zoledronate	Mandible	Chronic osteomyelitis
8	54	M	Prostate cancer	Zoledronate	Mandible	Chronic osteomyelitis
9	43	F	Breast cancer	Pamidronate	Mandible	Chronic osteomyelitis
10	67	F	Breast cancer	Zoledronate	Maxilla	Chronic osteomyelitis
11	83	F	Breast cancer	Zoledronate	Mandible	Chronic osteomyelitis
12	61	F	Breast cancer	Pamidronate	Maxilla	Chronic osteomyelitis

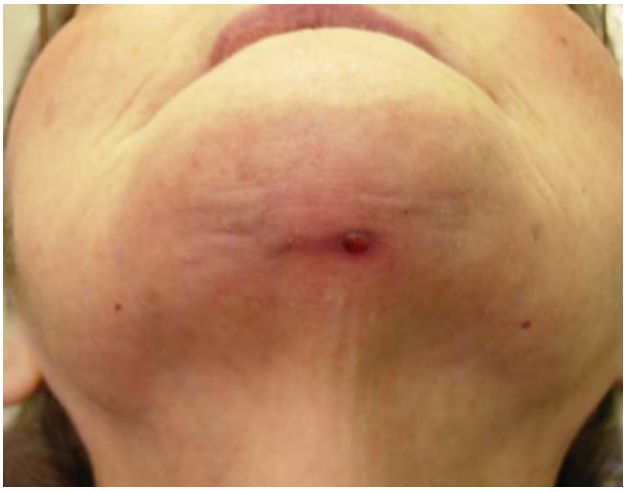

Figure 2. Draining oral cutaneous fistula from infected exposed necrotic bone of the mandible in the oral cavity.

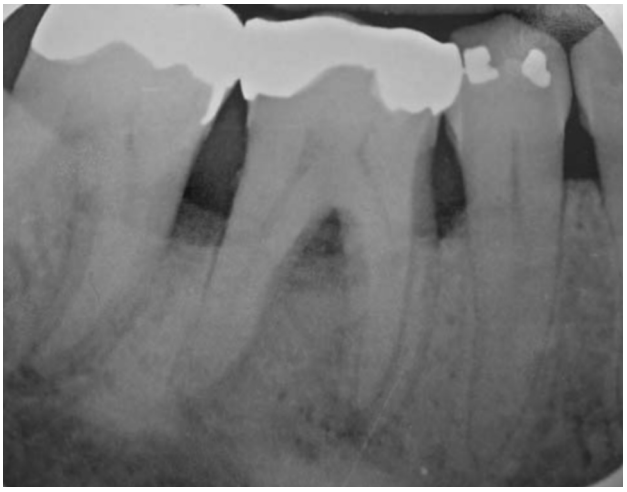

Figure 3. Bone loss in the root furcation around molars is an early sign of osteonecrosis of the jaw. This patient also had exposed necrotic bone on the lingual cortex of the mandible.

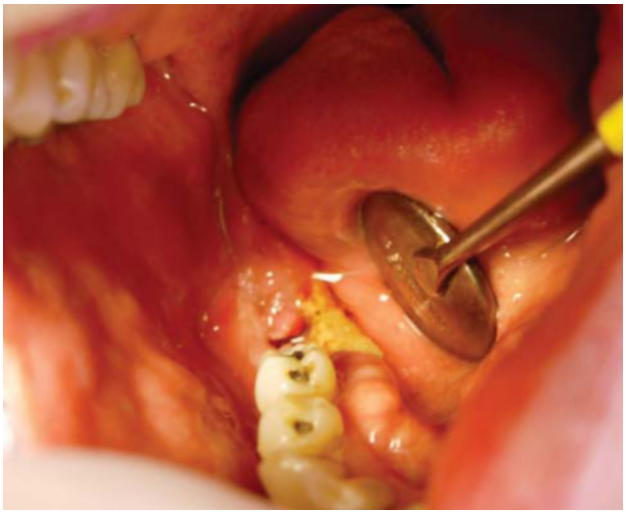

Figure 4. Spontaneously exposed necrotic bone over a mandibular torus. Mandibular tori are considered an anatomical comorbidity.

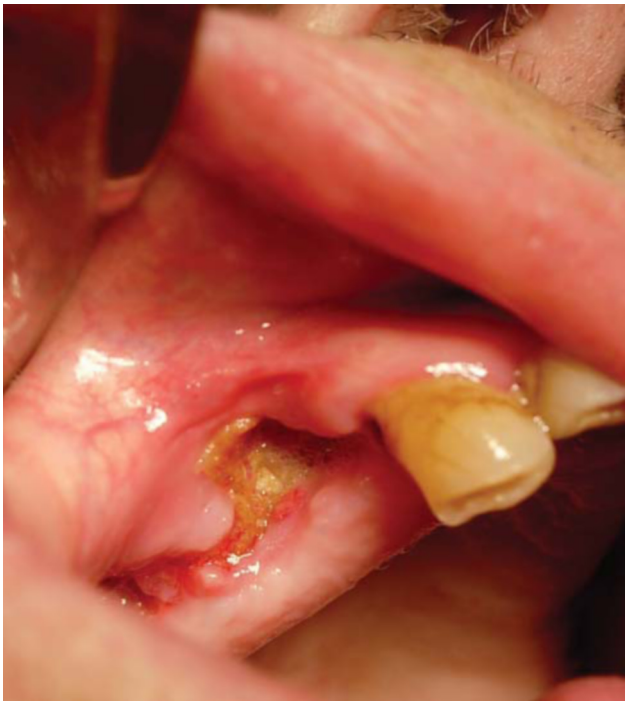

Figure 5. Exposed necrotic bone with mucosal ulceration in the maxilla precipitated by a tooth extraction.

(25 percent) had swelling, mobile teeth and a draining oral cutaneous fistula (Figure 2). In nine patients, panoramic radiography showed osteolytic changes. Three patients had a widened periodontal ligament in the root furcation around the molars (Figure 3). Bone exposure was more frequent in the mandible than in the maxilla. The posterior mandible in the molar region was the most common site of bone exposure (Figure 4). We saw bone exposure exclusively in the mandibles of nine patients (75 percent) and in the maxillas of three patients (25 percent).

Our patients had such comorbidities as underlying malignant disease, chemotherapy protocols and use of dexamethasone. We administered a variety of treatment regimens; concomitant bisphosphonate therapy was the only common denominator in these cases. Periodontal disease, which we found by means of clinical and radiographic examinations, was the most common dental comorbidity. We saw periodontitis with alveolar bone resorption in 11 patients (92 percent). Only two patients (17 percent) had a completely edentulous arch with exposed bone. We identified a precipitating event in nine cases (75 percent): six (50 percent) were related to dental extractions (Figure 5), two (17 percent) to

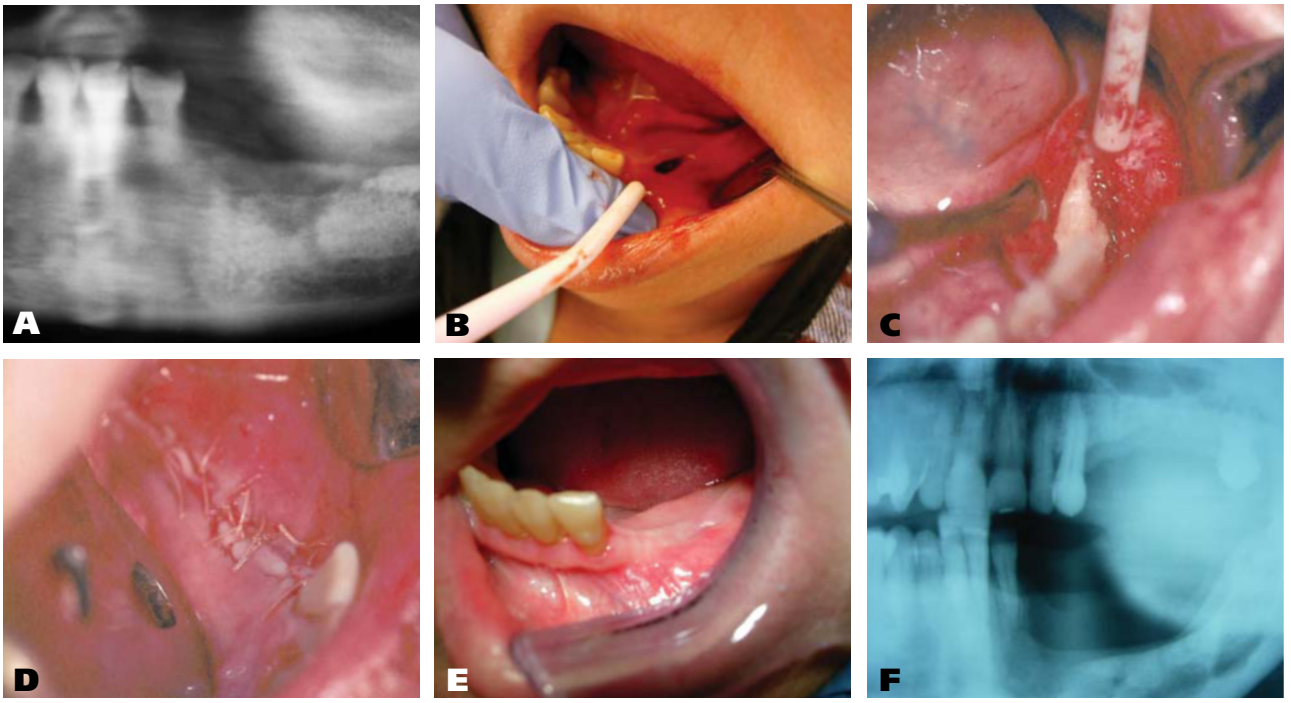

Figure 6. A. Panoramic radiograph demonstrating diffuse osteolytic changes in the mandible of a patient with refractory bisphosphonate-associated osteonecrosis. **B.** Intraoral clinical view showing exposed necrotic bone and mucosal dehiscence. **C.** Marginal mandibulectomy of the left side of the mandible to remove necrotic bone. **D.** Intraoral view of the left side of the mandible primarily closed after the application of platelet-rich plasma (PRP). **E.** Intraoral view showing complete mucosal healing at the surgical site six months after bone resection and application of PRP. **F.** Panoramic radiograph six months after marginal resection of the left side of the mandible showing partial bone healing.

advanced periodontal disease and one (9 percent) to trauma from a prosthesis. Three patients developed exposed necrotic bone spontaneously without any apparent periodontal disease, trauma or treatment.

DISCUSSION

Bisphosphonate osteonecrosis is a new oral complication of cancer treatment. Bisphosphonate therapy can be a vital component of a patient's chemotherapy regimen, and it is used increasingly to treat multiple myeloma, metastatic tumors (breast, lung, prostate) in the bones, osteoporosis, Paget disease and hypercalcemia of malignancy. Bisphosphonates are nonmetabolized analogues of pyrophosphate that have a high affinity for calcium. Bisphosphonates accumulate in the mineralized bone matrix in bone across extended periods, and they are internalized by osteoclasts, which cause a disruption in the osteoclastic bone resorption, which means they are osteoclastic activity inhibitors.[4] Physiological bone remodeling and deposition are compromised in patients who are receiving bisphosphonate therapy. Depending on the duration of treatment and the specific bisphosphonate agent, the drug may remain in the bone for years.[5] The exact mechanism of action of these drugs that leads to BON is unclear.

In 2003, Marx[2] reported BON in 36 patients who had painful bone exposure in the mandible and maxilla that was unresponsive to surgical débridement. All of the patients in his report had received pamidronate (Aredia, Novartis Pharmaceuticals, East Hanover, N.J.) and zoledronate (Zometa, Novartis Pharmaceuticals) therapy. In 2004, Ruggiero and colleagues[3] reviewed 63 cases of exposed bone in the jaws of 56 patients who had received bisphosphonates intravenously for at least one year and in the jaws of seven who were currently receiving oral bisphosphonate therapy. Treatment strategies included local surgical débridement, bone curettage, local irrigation with antibiotics and hyperbaric oxygen.[3,6] Many of these patients had poor outcomes despite therapy, and they experienced extensive dehiscence and increased bone exposure.[7] The inability to manage exposed bone lesions has compromised the nutritional, oncologic and oral care of patients with BON.

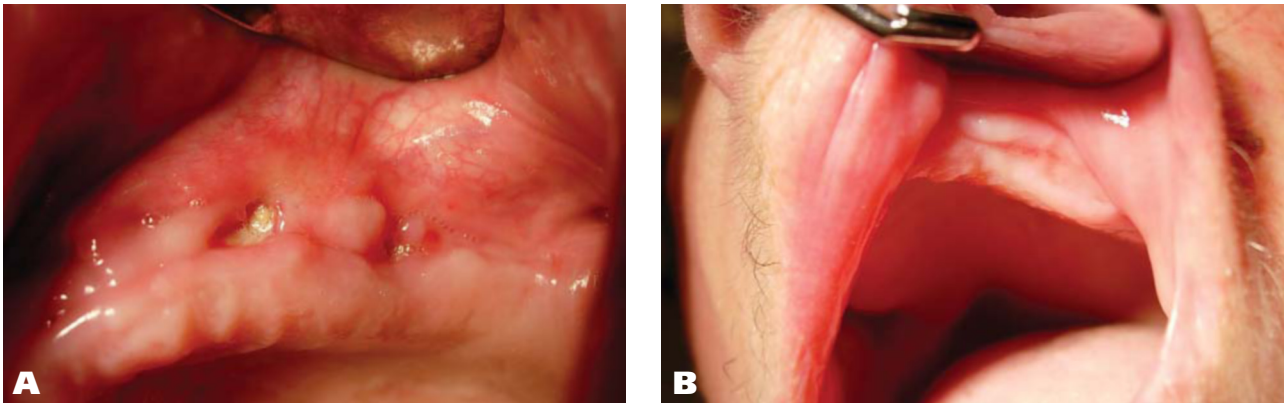

Figure 7. A. Intraoral view of a patient with refractory bisphosphonate-associated osteonecrosis in the maxilla with exposed necrotic bone. **B.** Intraoral view showing complete mucosal healing at the surgical site in the maxilla four months after bone resection and application of platelet-rich plasma.

The treatment of BON is challenging and difficult over an extended period. Most treatment has been ineffective in achieving complete wound healing, so prevention of this condition has been of paramount importance. Although complete prevention is not possible, the incidence of BON is reduced in patients who undergo a thorough dental evaluation before receiving bisphosphonate therapy. Avascular osteonecrosis has been refractory to most treatments.[2,3,8-10] Results of earlier studies showed that hyperbaric oxygen therapy does not improve wound healing or stimulate bone regeneration.[3,11] We have treated patients who have refractory BON with a combination of bone resection, topical application of PRP and placement of a resorbable membrane (Figures 6 and 7). The surgical approach includes a marginal resection of affected bone extended to an identified area of bleeding bone during removal of necrotic bone. BON was limited to the alveolar bone in these cases, thereby making it possible to maintain cortical bone for the integrity of the jaw.

Cellular mediators are effective in healing bone and soft-tissue defects.[12,13] PRP is an autologous concentration of human platelets, which are a source of growth factors for improved healing, angiogenesis and bone healing.[12-14] When the platelets are activated, they release protein growth factors such as PDGF, transforming growth factor-beta, vascular endothelial growth factor and epidermal growth factor-beta to stimulate precursor cells and enhance healing. PRP application in autogenous bone grafts, reconstructive surgery, implant surgery and soft-tissue grafts has a positive effect on soft-tissue, vascular and bone regeneration. PRP benefits wound healing, but it has not been reported as a treatment for BON in the literature. Osteonecrosis is a disease of biological disruption, so growth factors may be beneficial in facilitating wound healing in cases of osteonecrosis.

Vascular insufficiency due to thrombosis is associated with the development of osteonecrosis of the jaws,[15] and it occurs as a result of diminished arterial flow, increased intraosseous venous pressure and osseous hypoxia. Ruggiero and colleagues[3] found that the pathogenesis of osteonecrosis of the jaw most likely was localized vascular insufficiency. BON of the jaws not only forms from lack of bone turnover and remodeling but also may result from the loss of osseous cellular elements and vascular injury that leads to bone ischemia.

Experimental evidence indicates that zoledronate and pamidronate inhibit osteoclastic activity and capillary neoangiogenesis. Pamidronate has been reported to depress bone vascularity in rats.[6] This decreased vascularity is caused by the negative interaction of pamidronate with insulinlike growth factor I and growth hormone, both of which are integral in the regulation of blood flow in bone.[6,16] Fournier and colleagues[17] have shown in vitro and in a rat model that bisphosphonates inhibit angiogenesis, vascular endothelial growth factor and new capillary growth. Endothelial cell growth may be inhibited in the jaws and result in loss of a capillary network and avascular necrosis of bone.

Bone regeneration and growth involve the complex interaction of osteoclasts, osteoblasts and vascularity combined with local and systemic factors. The exact repair mechanism of avascular osteonecrosis is unknown. We combined the mechanical effect of necrotic bone resection with

the physiological effect of osteoconductive factors such as PRP to achieve bone healing.

CONCLUSIONS

The well-established clinical benefit of bisphosphonate therapy for cancer patients outweighs the potential risk of developing BON. For example, bisphosphonate therapy has reduced morbidity from serious skeletal complications of bone metastases in cancer patients. Therefore, the primary focus of dental practitioners, oncologists and dental specialists should be on prevention by having patients complete any necessary dental treatment before they receive bisphosphonate therapy.

However, osteonecrosis of the jaw is a manageable risk with conservative or surgical intervention. In our study, we treated patients who had BON with a combination of osseous resection, PDGF and a resorbable membrane. This therapy showed favorable results, including complete wound healing in most patients. In addition, this modality reduced these patients' treatment periods and gave them a better quality of life by decreasing pain. Although the findings of our report are not conclusive, we provide an effective treatment for refractory cases of BON that might be a useful alternative to existing BON treatment strategies. A controlled, randomized, prospective study is necessary to confirm our experience. ■

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