

Prosthetic treatment during active osteonecrosis related to radiation and bisphosphonate therapy: A clinical report

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Osteonecrosis of the jaws following the use of bisphosphonate drugs has been reported in the literature. Presently, there is limited evidence to establish guidelines for the prosthetic management of patients with active osteonecrosis, a history of osteonecrosis, or medical history of using these medications. This clinical report reviews the current literature regarding bisphosphonate use, and reports the prosthetic treatment of an edentulous patient with active osteonecrosis who had a history of oral bisphosphonate use and jaw irradiation. (J Prosthet Dent 2006;96:7-12.)

Osteonecrosis of the jaws is a relatively infrequent condition that is commonly associated with the secondary effects of radiation therapy for the treatment of head and neck cancer.¹⁻³ Ruggiero and others⁴⁻⁶ have recently reported a link of osteonecrosis of either jaw to use of both the intravenous and oral bisphosphonate class of drugs. Additional studies report the incidence, etiology, and treatment strategies for this new form of osteonecrosis.⁷⁻⁹ Bisphosphonate drugs are intended to preserve and increase bone mass, and are used to treat certain cancer and bone disease patients.¹⁰⁻¹²

Cancer patients with bone metastases frequently experience pain, pathological fractures, spinal cord compression, and hypercalcemia.¹⁰ These complications are the result of various tumor-produced cytokines, which can affect osteoclasts, the cells responsible for bone resorption.¹¹ By inhibiting osteoclastic activity, bisphosphonates can decrease the frequency of osteolytic lesions in patients with metastatic cancer.^{10,13} Bisphosphonates have also been shown to reduce bone pain, hypercalcemia, and skeletal complications in this patient population.^{14,15} The use of intravenous bisphosphonates is currently indicated for treatment of moderate to severe hypercalcemia associated with malignancy, as well as prevention of metastatic and osteolytic lesions associated with breast cancer, multiple myeloma, and solid tumors.⁴

The epidemic of osteoporosis in the elderly population of Western cultures has resulted in an increase in the use of oral bisphosphonates.¹⁶ A large randomized trial has shown that bisphosphonates can prevent osteoporosis and reduce the risk of hip fracture.¹⁷ As a consequence, oral bisphosphonates are among the most

commonly prescribed drugs in the United States.⁸ Bisphosphonates are also used in the management of other metabolic bone diseases, such as Paget's disease of bone, osteogenesis imperfecta, juvenile osteoporosis, and fibrous dysplasia.¹²

Bisphosphonates are analogs of pyrophosphate that have an affinity for bone. They reduce osteoclast activity, thereby decreasing bone resorption.^{4,6} The exact mechanism has not been fully described, but it is known that osteoclastic activity may be reduced at the bone surface,¹⁸ osteoclastic recruitment may be inhibited,¹⁹ and programmed cell death (apoptosis) of osteoclasts may be induced by bisphosphonates.²⁰ Bisphosphonate therapy can result in dense bone with the characteristics of osteopetrosis (marble bone disease).¹² Since bisphosphonates are not readily metabolized, they may persist in bone with potential long-term suppression of osteoclasts.⁴ Discontinuing the drug before dental treatment has not been demonstrated to reduce the risk of osteonecrosis, as the drug has been shown to persist in human bone for up to 12 years.²¹

Bisphosphonate drugs are classified according to use and method of delivery. The higher-potency bisphosphonates used for cancer management are generally injected. The most commonly used in North America are pamidronate (90 mg infused over 2 hours every 3 to 4 weeks) and zoledronate (4 mg infused over 15 minutes).¹⁵ However, the bisphosphonates used for the treatment of osteoporosis are taken orally. These drugs have a relatively low bioavailability; only about 1% to 2% of an oral dose is absorbed.^{15,22} The most commonly used oral products are alendronate (70 mg once weekly or 10 mg daily), sometimes compounded with colecalciferol,²³ and risedronate (35 mg once weekly or 5 mg daily).²⁴ The relative risk of osteonecrosis is higher in the cancer patient taking injectable bisphosphonates than it is in the osteoporosis patient on oral bisphosphonates.⁴ This clinical report presents the prosthetic management of a patient with osteonecrosis of the

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mandible and a history of oral bisphosphonate use, as well as irradiation of the mandible for cancer therapy.

CLINICAL REPORT

This clinical report was conducted in compliance with the Wayne State University Human Investigation Committee, and this patient was included in a previous publication describing a series of bisphosphonate-related osteonecrosis patients.⁹ A 64-year-old black woman was referred to the Maxillofacial Prosthetic Clinic at Wayne State University for evaluation for maxillary and mandibular complete dentures. Twenty-two months prior to the exam the patient was diagnosed with a Stage IV (T3, N2A, M0)²⁵ squamous cell carcinoma of the right floor of the mouth and tongue. The patient was treated with the surgical resection of the right floor of the mouth, including a right partial glossectomy, right modified radical neck dissection, and left supraomohyoid neck dissection. One of 55 lymph nodes recovered from the neck dissections was positive for squamous cell carcinoma. Reconstruction was accomplished with a split-thickness skin graft. The mandible was not involved in the surgery.

Six weeks following head and neck cancer surgery, the patient had all 30 teeth extracted in preparation for radiation therapy. A full-thickness mucoperiosteal flap was raised from all the teeth, and they were removed without complication. The bone was shaped to a smooth contour with primary flap closure. Radiation therapy was initiated 19 days following the extractions. The radiation treatment used a 3-field technique with a combination of 4 MV photon and 9 MeV electron beams. A dose of 6,000 cGy was delivered in 30 fractions over 6 weeks with concurrent chemotherapy (2 courses of carboplatin). The follow-up radiation therapy and chemotherapy were completed 17 months prior to the prosthodontic evaluation.

Other medical history included Type 2 diabetes mellitus for 8 years, hypertension, complete hysterectomy (nonmalignant) 12 years prior, and left breast cancer 2 years prior to the cancer of the floor of the mouth. Treatment for the breast cancer included lumpectomy and radiation treatment. Medications at the time of the initial evaluation included isophane insulin and regular insulin injection (30 units in the morning and 10 units in the evening), anastrozole (1 mg per day), amlodipine (5 mg per day), enalapril (10 mg per day), and ranitide (150 mg per day). The patient also had been taking a bisphosphonate, alendronate (10 mg per day), orally for 9 years to prevent osteoporosis.

The initial prosthodontic examination revealed hyperpigmentation of the skin bilaterally over the body of the mandible consistent with a history of radiation therapy, and changes in the right neck consistent with a history of neck dissection. Intraoral findings

included edentulous maxillary and mandibular arches, and postsurgical alteration of the right floor of the mouth, lingual vestibule, and tongue. An area of exposed bone measuring approximately 4 to 5 mm with irregular, inflamed soft tissue margins was seen on the right posterior lingual mandible in attached mucosa (Fig. 1). The area of exposed bone was asymptomatic. In the maxillary arch, a midline palatal torus and bilateral posterior buccal alveolar ridge exostoses were noted (Figs. 2 and 3). There was an asymptomatic fistula at the crest of the left posterior maxillary alveolar ridge. Maximum opening of the mandible was 35 mm as measured between the anterior edentulous ridges. The panoramic radiograph confirmed complete edentulism, no radiographic evidence of changes in the area of exposed bone, and a retained root fragment in the area of the maxillary left second molar. This related to the fistula noted on the residual ridge.

The initial clinical diagnosis was spontaneous osteoradionecrosis involving the right lingual mandible. The patient was referred back to the head and neck surgeon for evaluation and biopsy to rule out possible recurrence of cancer. The biopsy of the soft tissue margin was negative for recurrent cancer. The patient was then placed on a strict oral hygiene regimen to clean and irrigate the area of exposed bone with warm dilute saline. This regimen was continued for 2 months with no improvement; the area of exposed bone increased in size during this period.

Hyperbaric oxygen (HBO) treatment was prescribed per the Robert Marx protocol.²⁶ This protocol uses HBO and aggressive surgery in a progressively staged manner to treat osteoradionecrosis (ORN). Stage I patients have osteoradionecrosis but without pathological fracture, orocutaneous fistula, or radiographic evidence of bone resorption to the inferior border of the mandible. Patients receive 30 HBO treatments (2.4 atmospheres, 100% oxygen for 90 minutes). If at the end of the 30 treatments there is clinical evidence of improvement, another 20 treatments are added. If no clinical improvement is seen, the patient is considered a nonresponder and advanced to stage II.

Stage II nonresponders have a surgical sequestrectomy with primary closure. An additional 10 HBO treatments are given. If the wound dehisces, the patient is determined to be a nonresponder and advanced to stage III. Nonresponders from stage II and patients presenting with orocutaneous fistula, pathological fracture, or radiographic evidence of bone resorption to the inferior border of the mandible are considered stage III patients. The involved nonvital mandibular bone is resected transorally, and fixation of the mandibular segments is achieved. Soft tissue deficits are restored with local and distant flaps. Another 10 HBO treatments are given and the patient is advanced to stage IIIR. For Stage IIIR patients, 10 weeks after resection, the mandible is

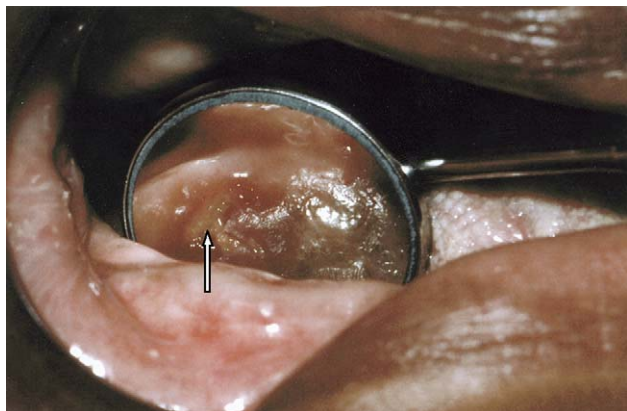


Fig. 1. Clinical presentation of osteonecrosis with inflamed soft tissue margins on lingual mandible. Note exposed bone in left lower quadrant of mirror image (*arrow*).



Fig. 2. Midline palatal torus and left posterior buccal alveolar ridge exostosis.



Fig. 3. Right posterior buccal alveolar ridge exostosis. Copious saliva was positive factor for maxillary denture retention.

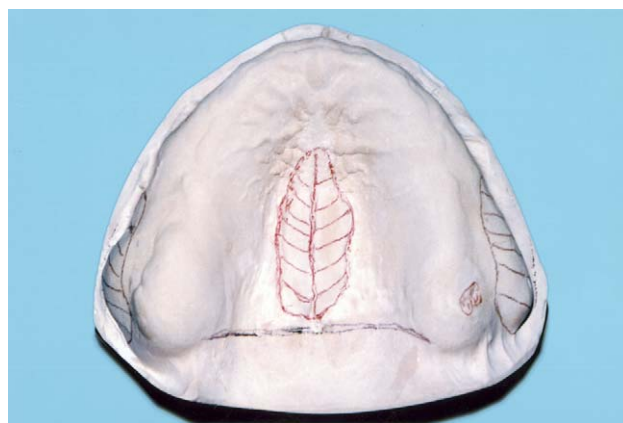


Fig. 4. Midline palatal torus highlighted by *red lines* as is fistula on superior aspect of posterior left alveolar ridge. Buccal alveolar ridge exostoses are marked with *brown lines* (at left and right). Vibrating line is marked in *blue* (horizontally across lower portion).

reconstructed with a bone graft using a transcutaneous exposure.

Following the first 30 HBO treatments, the patient was referred back to the head and neck surgeon for local debridement of the exposed bone with no attempt at flap closure. Following the debridement, 10 additional HBO treatments were given.

Six weeks following completion of the HBO therapy, the area of exposed bone was greatly decreased in size, with near total soft tissue coverage. At 10-week follow-up, the area of exposed bone had nearly increased in size to its original presentation, with inflamed soft tissue margins, but remained asymptomatic. A new panoramic radiograph confirmed no radiographic evidence of changes in the area of exposed bone. The clinical presentation and radiographic findings were not consistent for patients with initial minimally involved ORN following stage II HBO treatment. The uncharacteristic response of the exposed bone to HBO changed the clinical diagnosis from solely spontaneous osteoradionecrosis, to

osteonecrosis related in part to bisphosphonate toxicity. The patient's primary care physician was consulted, and the patient was removed from the oral bisphosphonate therapy involving alendronate.

The original prosthodontic treatment plan included preprosthetic surgery to include extraction of the retained maxillary root fragment, reduction of the midline palatal torus, and reduction of the largest posterior maxillary buccal alveolar ridge exostoses. This would allow for fabrication of conventional maxillary and mandibular complete dentures. The new clinical diagnosis of osteonecrosis related in part to bisphosphonate therapy, and the attendant potential for additional bisphosphonate-related osteonecrosis following preprosthetic oral surgery resulted in the development of a new prosthodontic treatment plan. The revised treatment plan included no mandibular denture, and an unconventional maxillary denture that would not engage the undercuts in the



Fig. 5. Processed maxillary complete denture refit to definitive cast.



Fig. 6. Intaglio surface of maxillary complete denture.



Fig. 7. Facial view with prosthesis in place. Asymmetry of lower lip and neck are due to surgical and radiation treatment for cancer of tongue and floor of mouth and are not related to bisphosphonate osteonecrosis.

areas of the exostoses and would have minimal or no contact with the palatal torus. The maxillary denture was intended to improve dental facial appearance and speech, but provide no masticatory function. The patient was fully informed regarding the adverse bone response and potential for additional problems if a

mandibular denture were made or if surgical procedures were performed in the maxillary arch. The patient was also advised regarding the limitations of the maxillary denture and possible need for the use of denture adhesive. The patient accepted the treatment plan.

An oversized metal, nonperforated stock dentate impression tray (Rim-Lock; Dentsply Caulk, Milford, Del) was used to make an irreversible hydrocolloid (Jeltrate Plus; Dentsply Caulk) preliminary impression of the maxillary arch. The impression was cast in Type III stone (Labstone (Buff); Heraeus Kulzer, Armonk, NY) (Fig. 4). An outline for a record base (Hygon tray material; Hygenic Corp, Akron, Ohio) was developed on the cast. The midline palatal torus and undercuts were blocked out with wax (Baseplate wax, Type II regular; Dentsply Intl, York, Pa). Subsequently, a record base and wax occlusion rim were contoured at chairside in preparation for arranging teeth. Teeth of the selected size, form, and shade (Trubyte; Dentsply Intl) were arranged for trial insertion. Appearance, speech, midline, plane of occlusion, and nonfunctional contact with the mandibular edentulous ridge were verified. The nonfunctional contact with the mandibular edentulous ridge was verified by placing disclosing wax (Disclosing wax, Ivory; Kerr, Romulus, Mich) on the incisal edges and occlusal surfaces of the teeth and posterior base of the denture. The patient was instructed to speak and swallow, and the areas covered with wax were inspected to ensure no pressure or perforation of the wax.

The patient was pleased with the appearance and speech at the clinical trial insertion. The record base was retentive and required no denture adhesive for trial insertion. The denture was processed using heat-polymerizing polymethyl methacrylate (Lucitone 199; Dentsply Intl) on a duplicate cast of the blocked out definitive cast. The processed maxillary complete denture was adjusted and finished to fit the definitive cast (Figs. 5 and 6). The denture was inserted with the use of pressure indicating paste made in the office (Zinc

oxide ointment [1 oz]; Fougera, Melville, NY; zinc oxide paste [1 oz]; Boudreaux's, Covington, La; eugenol [2 drops]; Sultan Dental Products Ltd, Englewood, NJ; Argo corn starch [1 tsp]; Bestfood, Englewood Cliffs, NJ). At the time of the preparation of this report the patient had been followed for 2 months postinsertion. She was pleased with the outcome and has not had to use denture adhesive (Fig. 7). The exposed bone, although slightly smaller, persists in the mandible.

DISCUSSION

The initial clinical diagnosis for this patient was spontaneous osteoradionecrosis. However, the uncharacteristic response to HBO treatment and surgical debridement did not fully support this sole diagnosis. Potential risk factors that may increase the risk of osteonecrosis of the jaws in patients being treated with bisphosphonates include radiation therapy, dental extraction, infectious disease, dental trauma, concomitant therapy with corticosteroids, and chemotherapy.²⁷ The potential additive effect of altered bone metabolism due to radiation therapy and bisphosphonate use was considered in this patient. This consideration resulted in the diagnosis of osteonecrosis related in part to bisphosphonate therapy. The clinical evidence of altered bone metabolism in light of the patient's medical history, current medical diagnosis, and medications all contributed to the clinical diagnosis and altered prosthodontic treatment plan.

Presently, there is little evidence to direct the prosthodontic management of patients with a history of bisphosphonate use, although more problems have been associated with intravenous bisphosphonates than oral forms.⁴ Patients on oral bisphosphonate therapy for management of osteoporosis appear to be at substantially lower risk of osteonecrosis than patients receiving intravenous bisphosphonate therapy for management of cancer. However, it is unclear how much of this difference is due to the method of delivery of this medication, and how much is due to differences in the health and previous medical therapies between the otherwise healthy osteoporotic patients and the cancer survivors. The patient in this report demonstrates the multifactorial nature of osteonecrosis that can be occasionally seen in clinical practice. This patient was a 2-time cancer survivor who had been treated with radiation therapy and also an osteoporosis patient who had been treated with bisphosphonate. Additionally, the patient is an insulin-dependent diabetic with medical/pharmaceutical management of high blood pressure.

Patients with active osteonecrosis related to bisphosphonate use demonstrate the clinical manifestations of the underlying altered metabolism of bone. For these patients, it is not unrealistic to expect reduced tissue tolerance to function with removable prostheses and decreased potential for osseointegration of dental

implants.^{28,29} Decisions regarding continued use of a current prosthesis, fabrication of a new prosthesis, or performing any invasive surgical procedures are based on clinical judgment tempered by the presenting conditions, medical profile, and patient needs. These are the factors that determined the conservative prosthodontic treatment for this patient. Until further evidence emerges regarding management of patients with active bisphosphonate-related osteonecrosis, conservative prosthodontic treatment is reasonable and prudent.

SUMMARY

The development of osteonecrosis of the jaws related to the use of the bisphosphonate class of drugs is a recently recognized side effect. The past or present use of this class of drugs should be established from the patient's health history. The treating clinician should be aware of osteonecrosis as a potential complication and consider relative risks dependent on the form of bisphosphonate therapy (intravenous or oral) and indication for use (cancer or osteoporosis). Additional predisposing factors should also be considered, such as previous jaw irradiation, and the possibility that multiple factors may increase risk should be considered, although it has not been proven at present. If active osteonecrosis is identified, referral to an oral and maxillofacial surgeon or other dental specialist for potential biopsy and management may be indicated. The clinician should be cautious regarding treatment, and conservative prosthodontic intervention for tissue-borne prostheses is recommended for patients with active osteonecrosis, regardless of the predisposing factors.

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Noteworthy Abstracts of the Current Literature

Nonalloyed titanium as a bioinert metal—A review

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Titanium is used for many dental applications and instruments, such as orthodontic wires, endodontic files, dental implants, and cast restorations. The popularity of titanium is primarily due to its good mechanical properties, its high corrosion resistance, and its excellent biocompatibility. A thorough review of the medical and dental literature reveals, however, that titanium can also cause chemical-biological interactions. Tissue discoloration and allergic reactions in patients who have come in contact with titanium have been reported. The biostability of titanium is becoming increasingly questioned. At the same time, new technologies and materials, such as high-performance ceramics, are emerging which could replace titanium in dentistry in the not-too-distant future.—*Reprinted with permission of Quintessence Publishing.*