

- If surgery is required in patients with established osteonecrosis, cessation or interruption of bisphosphonate therapy may be considered taking into account the potential risk of further osteonecrosis versus the risk of skeletal complications or hypercalcemia of malignancy. It is unknown whether or not there is benefit to cessation of bisphosphonate therapy. However, cessation of bisphosphonate therapy may be prudent in some patients if the risk of osteonecrosis outweighs the risk of skeletal complications or hypercalcemia of malignancy. Therefore, the decision to stop bisphosphonate therapy must be coordinated between the treating oncologist and an oral surgeon. Antibiotics following dental surgery may be appropriate in this patient population and should be continued postoperatively for at least 10 days. However, this is a clinical judgment that must be made in collaboration with the treating oncologist. Cultures taken from the extraction site at the time of oral surgery can provide guidance in making this decision
- Hyperbaric oxygen has not been shown to be effective and, therefore, is not recommended
- Osseointegrated dental implants are contraindicated and may result in further osteonecrosis

References

1. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg.* 2003;61:1115-1117.
2. Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol.* 2003;21:4253-4254.
3. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg.* 2004;62:527-534.

* The expert panel representatives were as follows: **Kathryn Damato, RDH, MS, CCRP**, University of Connecticut Health Center, Farmington, Conn; **Julie Gralow, MD**, University of Washington Medical Center, Seattle, Wash; **Ana Hoff, MD**, University of Texas MD Anderson Cancer Center, Houston, Tex; **Joseph Huryn, DDS**, Memorial Sloan-Kettering Cancer Center, New York, NY; **Robert Marx, DDS**, University of Miami School of Medicine, Miami, Fla; **Salvatore Ruggiero, DMD, MD**, Long Island Jewish Medical Center, New Hyde Park, NY; **Mark Schubert, DDS, MDS**, Seattle Cancer Care Alliance, Seattle, Wash; **Bela Toth, DDS, MS**, University of Texas MD Anderson Cancer Center, Houston, Tex; **Vicente Valero, MD, FACP**, The University of Texas MD Anderson Cancer Center, Houston, Tex.

Background

Osteonecrosis of the jaws is a rare potential complication in cancer patients receiving radiation, chemotherapy, or other cancer treatment regimens, or in patients with tumors/infectious embolic events. Recently, there have been reports of osteonecrosis of the jaws in cancer patients receiving concomitant anticancer therapy (chemotherapy, steroid therapy, or head and neck radiotherapy) and an intravenous (IV) bisphosphonate.^{1,3} There are multiple recognized conditions and risk factors associated with the development of osteonecrosis (not limited to the jaws) in cancer patients. These factors include trauma, female sex, advanced age, edentulous regions, combination cancer therapy (eg, head and neck radiotherapy, chemotherapy, or steroid therapy), blood dyscrasias/metastatic disease, anemia, coagulopathy, surgical dental procedures, alcohol or tobacco use, and prior infection. In the cases reported to date, the majority of patients were receiving long-term chemotherapy and many were receiving short-term intermittent steroid therapy with concomitant bisphosphonate therapy for their cancer and symptom management. In the majority of cases, patients could be managed in a pain-free state with continued exposed bone using a nonsurgical approach consisting of oral systemic antibiotics and 0.12% chlorhexidine gluconate antiseptic-containing oral rinses. Surgical intervention was counterproductive and often produced further exposed bone. Bisphosphonates and other cancer therapies were continued in the majority of patients.

A causal relationship between bisphosphonate therapy and osteonecrosis of the jaws has not been established. However, to better understand the pathogenesis of and management of patients with osteonecrosis of the jaws, a panel of experts* representing oral surgery, oral medicine/oral oncology, endocrinology, and medical oncology convened recently to discuss identification of risk factors for osteonecrosis of the jaws, and to develop clinical guidelines for prevention, early diagnosis, management, and multidisciplinary treatment of osteonecrosis of the jaws in patients with cancer. Additionally, the panel developed recommendations to reduce the incidence of osteonecrosis of the jaws in cancer patients receiving bisphosphonate therapy as well as for patients with clinical osteonecrosis of the jaws who are already receiving bisphosphonates and may require oral surgery. The panel's recommendations are presented here to help guide physicians in patient management.

Clinical Presentation and Diagnosis of Osteonecrosis of the Jaws

- Osteonecrosis of the jaws may remain asymptomatic for many weeks or months and may only be recognized by the presence of the exposed bone in the oral cavity. These lesions are most frequently symptomatic when sites become secondarily infected or there is trauma to the soft-tissues via the sharp edges of the exposed bone
- Typical signs and symptoms include pain, soft-tissue swelling and infection, loosening of teeth, drainage, and exposed bone, which may occur spontaneously or, more commonly, at the site of previous tooth extraction. Some patients may present with atypical complaints, such as "numbness," the feeling of a "heavy jaw," and various dysesthesias
- Signs and symptoms that may occur before the development of clinical osteonecrosis include a sudden change in the health of periodontal or mucosal tissues, failure of the oral mucosa to heal, undiagnosed oral pain, loose teeth, or soft-tissue infection
- If osteonecrosis is suspected, panoramic and tomographic imaging may be performed to rule out other etiologies (eg, cysts or impacted teeth). Smaller intraoral films can also be used to demonstrate subtle bone changes
- Microbial cultures may provide a differential diagnosis for comorbid oral infections
- Tissue biopsy should be performed only if metastatic disease is suspected. If a biopsy is performed to rule out metastatic tumor, microbial cultures (aerobic and anaerobic) may provide identification of the pathogens causing secondary infections (Note: actinomyces organisms are often seen microscopically or identified upon culture)

Potential Risk Factors for the Development of Osteonecrosis of the Jaws

- The precise risk factors for osteonecrosis of the jaws have not been identified. Risk factors may include
 - Concomitant therapy with steroids, chemotherapy, and IV bisphosphonates (in few instances after short dosing)
 - Dental extraction, infectious disease, and/or trauma
 - Occasionally the concomitant risk factors may not be apparent
- Other risk factors that have been previously identified for osteonecrosis (not limited to the jaws) include
 - Head and neck radiotherapy, chemotherapy, immunotherapy, or other cancer treatment regimens
 - Female gender, coagulopathies, infections, periodontal disease, bony exostosis, previous invasive dental procedures, dental prostheses, arthritis, blood dyscrasias, vascular disorders, alcohol abuse, smoking, and malnutrition. Controversially, anesthetics with vasoconstrictors (ie, novocaine) have been reported as potentially contributing to some cases of osteonecrosis

Potential Preventive Measures Prior to the Initiation of IV Bisphosphonate Therapy

- Avoid any elective jaw procedure that will require bone to heal
- Recommend a routine clinical dental exam that may include a panoramic jaw radiograph to detect potential dental and periodontal infections
- If bisphosphonate therapy can be briefly delayed without the risk of a skeletal-related complication, teeth with a poor prognosis or in need of extraction should be extracted and other dental surgeries should be completed prior to the initiation of bisphosphonate therapy. The benefit or risk of withholding bisphosphonate therapy has not been evaluated to date. Therefore, the decision to withhold bisphosphonate treatment must be made by the treating oncologist in consultation with an oral maxillofacial surgeon or another dental specialist
 - Suggested preventive dentistry before initiation of chemotherapy, immunotherapy, and/or bisphosphonate therapy may include
 - Remove abscessed and nonrestorable teeth and involved periodontal tissues
 - Functional rehabilitation of salvageable dentition, including endodontic therapy
 - Dental prophylaxis, caries control, and stabilizing restorative dental care
 - Examine dentures to ensure proper fit (remove dentures at night)
 - Oral self-care hygiene education
 - Prophylactic antibiotics are not indicated before routine dentistry unless otherwise required for prophylaxis of bacteremia in those patients at risk (eg, those with an indwelling catheter)
- Educate patients regarding the importance of good dental hygiene and symptom reporting
 - Suggest regularly scheduled hard- and soft-tissue oral assessments, possibly every 3 to 4 months, depending on risk
- Oncologists should perform a brief visual inspection of the oral cavity at baseline and at every follow-up visit

Dental Treatment for Patients Currently Receiving Bisphosphonate Therapy

- Maintain excellent oral hygiene to reduce the risk of dental and periodontal infections
- Check and adjust removable dentures for potential soft-tissue injury, especially tissue overlying bone
- Perform routine dental cleanings, being sure to avoid soft-tissue injury
- Aggressively manage dental infections nonsurgically with root canal treatment if possible or with minimal surgical intervention
- Endodontic (root canal) therapy is preferable to extractions when possible. It may be necessary to carry out coronal amputation with subsequent root canal therapy on retained roots to avoid the need for tooth extraction and, therefore, the potential development of osteonecrosis

Management of Patients With Osteonecrosis of the Jaws

- Consultation with an oral surgeon or dental oncologist
- A nonsurgical approach may prevent further osseous injury
 - Minimal bony debridement only to reduce sharp edges so as to reduce trauma to surrounding or opposing tissues (eg, lateral tongue where lingual mandibular bone is exposed)
 - A removable appliance may be used to cover and protect the exposed bone
 - A protective stint may be of benefit for patients with exposed bone that causes trauma to adjacent tissues and in patients where the osteonecrotic site is repeatedly traumatized during normal oral function. A thin, vinyl, vacuformed mouth guard or thin acrylic stint may be used, provided that the device does not further traumatize the osteonecrotic site and that it can be kept free of bacterial plaque and debris
 - Biopsy should be performed only if metastasis to the jaw is suspected. A portion of the biopsy should be submitted for microbial analysis as well as culture from the biopsy site
- Intermittent or continuous antibiotic therapy may be beneficial (cultures should be collected to determine the appropriate antibiotic therapy). The goal of antibiotic therapy is to prevent secondary soft-tissue infection and, therefore, pain as well as to prevent osteomyelitis. At this time, the duration of antibiotic therapy and the benefit of oral antiseptic rinses have not been defined, but pain control and disease control have been observed with this management strategy. The decision to treat with an antibiotic is a clinical judgment that should be made by an oral maxillofacial surgeon or other dental specialist in consultation with the treating physician/oncologist. Cultures, including those for aerobic, anaerobic, viral, and fungal species, may be collected to determine the appropriate antimicrobial intervention. Antibiotics that have been found useful for osteonecrosis include
 - Penicillin VK 500 mg or amoxicillin 500 mg; both 4 times daily (QID) initially and twice daily (BID) for maintenance
 - If penicillin allergic:
 - Clindamycin 150 to 300 mg QID
 - Vibramycin 100 mg once daily (QD)
 - Erythromycin ethylsuccinate 400 mg 3 times daily (TID)
 - Antifungals when required:
 - Nystatin oral suspension 5 to 15 mL QID or 100,000 IU/mL
 - Mycelex troches (clotrimazole 10 mg) × 5/day
 - Fluconazole 200 mg initially, then 100 mg QD
 - Other potential systemic antifungals include itraconazole or ketoconazole
 - Antivirals, if required:
 - Acyclovir 400 mg BID
 - Valacyclovir hydrochloride 500 mg to 2 g BID
- 0.12% chlorhexidine gluconate (Peridex®) oral rinses or minocycline hydrochloride (Arestin®) periodontal pockets can be used
- Dentures can be worn, but should be adjusted to minimize soft-tissue trauma or irritation, especially in light of ongoing antibiotic therapy, and should be removed at night
- All patients should be monitored every 3 months or sooner if symptoms continue or worsen
- Cessation or interruption of bisphosphonate therapy may be considered in severe cases. However, close coordination between the dental specialist and the medical oncologist is recommended, taking into consideration the risk of skeletal complications (including hypercalcemia of malignancy) versus the risk of osteonecrosis. To date, cessation of bisphosphonate therapy appears to have no effect on established osteonecrosis. However, further study is needed