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Osteonecrosis ONJ Session

Distinguishing features of the oral cavity and its predisposition to osteonecrosis

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Bisphosphonate use has increased over the past few years as it has been widely prescribed for the treatment of osteoporosis and for several types of cancers. The success of bisphosphonates in the treatment of skeletal metastasis has centered on their ability to inhibit bone resorption and hence alter the tumor microenvironment. Bisphosphonates have had a very positive impact as therapeutic agents but they have also been associated with osteonecrosis of the jaw (ONJ) which has emerged as an idiosyncratic oral complication. The penchant for ONJ affecting the bones of the oral cavity is intriguing and motivates consideration of the unique aspects of the bones of the craniofacial apparatus and their response to bisphosphonates.

There are many characteristics of the oral cavity that can be compared and contrasted to other bones of the human skeleton. The maxilla and mandible form primarily via intramembranous bone formation vs. the endochondral development of the long bones. The cortical bone of the mandible is particularly thick with the thickest dimension in the premolar and molar region, a site that is frequently affected by osteonecrosis. Vascular perforation of the mandibular cortical bone is less than that of the maxilla. Hematopoiesis, which typically occurs in the vertebrae, ribs and long bones, is very limited in the jaw with most of the bones being occupied by fatty marrow in adults. The presence of a hematopoietic environment is likely protective in the healing response of bone and its diminution may con-

tribute to the deleterious effects leading to osteonecrosis.

Wound healing in the oral cavity has been well characterized in regard to tooth extractions. Since many cases of ONJ are associated with surgical procedures and/or tooth extraction, the events associated with osseous healing post-extraction are valuable to consider. Soon after the extraction, a coagulum forms with the influx of red blood cells, platelets and neutrophils in a fibrin matrix. Next, a vascularized granulation tissue occupies the site and formulates the provisional matrix. This matrix is comprised of new blood vessels, immature mesenchymal cells, leukocytes and collagen fibers. Osteoclasts are recruited to the site to remodel the residual and adjacent borders of bone. New woven bone is formed and then remodeled with increased osteoclastic activity. The woven bone is replaced by lamellar bone that develops into mature trabeculae and bone marrow. A compromise in osteoclast function could render ineffective the early remodeling of the old lamellar bone and/or the later remodeling of the new woven bone. In support of this, studies of tooth extraction in osteopetrotic rodents have reported compromised healing, and humans with osteopetrosis often have compromised oral wound healing. The oral cavity is also subject to other traumas including surgical procedures for implant placement, the treatment of periodontal disease, biopsy procedures and non-surgical adverse events such as caused by ill-fitting prostheses, oral habits and inadvertent trauma.

The bones of the oral cavity provide a unique environment relative to blood flow and oral microbiota. Bisphosphonates have been reported to alter angiogenesis but it is not clear that the bones of the oral cavity have any greater propensity for altered angiogenesis. There are many sites in the oral cavity where the bone is covered by a thin layer of epithelium and with more than 500 different species of microorganisms capable of colonizing the oral cavity, trauma to the epithelium can result in a bacterial insult to the underlying osseous structures.

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Once ONJ is established there is noted difficulty in its resolution as many patients continue living with exposed bone for long periods of time and some permanently. However, the incidence of ONJ is very low. What could become more challenging is if there are compromises in healing that patients on bisphosphonates experience. Healthy patients heal normally after procedures such as a tooth extraction,

but it is not clear whether a patient on a bisphosphonate heals in the same manner, regardless of the presence of ONJ. Although little is known of the mechanisms and course of ONJ, even less is known about the spectrum of issues of altered healing that fall short of defined ONJ. Furthermore, the incidence of ONJ in non-bisphosphonate users has not been determined as a comparison.