BISPHOSPHONATE THERAPY, WOUND HEALING AND THE PATHOBIOLOGY OF OSTEONECROSIS OF THE JAW (ONJ)

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Bisphosphonates (BP) like Zometa (ZA) are widely used to treat complications of bony metastases in cancer patients, with 3 million patients receiving BP therapy worldwide. A serious adverse event occurs in 1-12% of patients on BP therapy, osteonecrosis of the jaw (ONJ). ONJ develops after oral trauma (tooth extractions) and is manifested by poor wound healing and soft-tissue breakdown followed by exposure and necrosis of intra-oral bone. Currently, there is no effective clinical treatment for ONJ. Oral wound repair is initiated by clotting and the formation of granulation tissue, followed by fibroblast migration into the wound, proliferation and deposition of collagen to increase wound strength. Fibroblast apoptosis leaves a collagen-rich environment that stimulates re-epithelization. Initially, epithelial cells migrate without proliferation, highlighting the requirement for a viable wound bed, then proliferate to generate additional migratory cells for wound re-epithelization. We evaluated the effect of ZA on the proliferation, apoptosis and migratory capacity of oral fibroblasts (CRL-7408) and oral epithelial cells (OKF6). ZA treatment inhibited the proliferation and enhanced apoptosis of oral fibroblasts, resulting in a significant reduction in the closure rate of a scratch wound. While proliferation of oral epithelium also was inhibited by ZA, motility was unaffected. This supports a model wherein ZA treatment impedes oral wound healing by blocking the growth and migratory capacity of oral fibroblasts, functions necessary to deposit the granulation tissue needed for re-epithelization. Therefore, BP released from bone following tooth extraction may delay wound healing of the oral mucosal barrier and contribute to ONJ pathogenesis.