Pharmacologic Modalities in the Treatment of Osteoradionecrosis of the Jaw

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KEYWORDS

• Osteoradionecrosis • Radiation-induced fibroatrophy • Pentoxifylline • Tocopherol • Clodronate

KEY POINTS

- Managing osteoradionecrosis (ORN) of the facial bones is a challenge in maxillofacial head and neck surgical practice.
- Changes in understanding of ORN of the jaws has led to new studies using novel therapeutic modalities to manage this disorder.
- These treatment regimens may allow medical management to replace major reconstructive surgery for some patients who have already undergone chemoradiotherapy or combined modality therapy for head and neck cancer.

INTRODUCTION

Osteoradionecrosis (ORN) of the jaws was first described in the 1920s and remains the most problematic complication occurring after the use of radiotherapy to treat head and neck cancer.[1] The condition has been defined as exposed and necrotic bone associated with ulcerated or necrotic soft tissue that persists for greater than 3 months in an area that has been previously irradiated, and is not caused by tumor recurrence.[2] According to the current medical literature, approximately 20.0% (range, 0.9%–35.0%) of patients have radiotherapy as part of their head and neck cancer treatment.[3] This incidence may be declining.[4] The condition affects the mandible most frequently, and diagnosis depends on clinical features, including a history of exposure to greater than 50 Gy of ionizing radiation. Symptoms include pain, trismus, and dysesthesia. Clinical signs include ulceration and/or necrosis of the oral mucosa, exposure of underlying bone, malodor, and, in advanced stages, ulceration of overlying skin and pathologic fracture.[5]

PATHOGENESIS

Four hypotheses have been described for the development of ORN. Watson and Scarborough[6] first described the sequence of radiation exposure, local injury, and infection as a possible cause, and this hypothesis was further popularized by Meyer.[7]

Later Marx[8] described the "Three-H" hypothesis: wherein the area shows a hypocellular, hypoxic, and hypovascular state. This condition is thought to be consequent to microvasculature damage, resulting in endarteritis, thrombosis, and vessel obliteration.

A more recently described hypothesis is that of suppression of osteoclast mediated bone turnover, wherein irradiation-induced loss of osteoclast function results in the clinical features described earlier. This idea is supported by the evidence from antiresorptive therapy–related osteonecrosis of the jaws, which occurs after administration of bisphosphonates and other antiresorptive agents in some patients.

Delanian and Lefaix[9,10] proposed a fourth hypothesis of fibroatrophic bone change in 2004

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based on enhanced understanding of the cellular and molecular biology of the histopathologic features seen in ORN. Earlier, in 1998, the first report emerged of bone healing in a patient with ORN of the sternum after receiving radiotherapy for carcinoma of the breast 29 years previously treated with pharmacologic therapy based upon this new hypothesis. With this hypothesis, bone and soft tissue damage is proposed to be caused by radiation-induced fibrosis, and this has been summarized by Lyons and Ghazali.[11] Three phases of tissue injury are described, which mirror those in healing of chronic traumatic wounds[12]: the initial predominantly acute inflammatory phase with endothelial changes, a second phase of abnormal fibroblast activity with extracellular matrix disruption, and a third late fibroatrophic phase. At this late phase, the healed tissues are friable and undergo late reactivation of the acute inflammatory response after injury.

In the proposed fibroatrophic mechanism, the key event in ORN progression is described as activation and dysregulation of fibroblast activity, resulting in tissue atrophy and fibrosis. Radiation-induced endothelial injury initiates cytokine release, including tumor necrosis factor α (TNF-α); fibroblast growth factor β; platelet-derived growth factor; interleukin (IL) 1, 2, and 4; connective tissue growth factor; and transforming growth factor β1 (TGF-β1). This process produces a predominance of the myofibroblast phenotype, with attendant high rates of cellular proliferation and release of abnormal extracellular matrix (ECM) components.[13] These myofibroblasts also demonstrate impaired ability to breakdown the abnormal ECM. This is shown diagrammatically in **Fig. 1**. This fibroblast process is similarly described in fibrotic processes in the lungs and liver after tissue injury of various types.[14]

Ionizing radiation produces osteoblast cell death and prevents repopulation of this cellular component of bone. Together with excess myofibroblast proliferation and abnormal ECM formation, a reduction in bony hard tissue matrix and an excess of fibrous tissue is described. Four possible mechanisms of bony destruction are suggested by Delanian and colleagues[15] in an article describing microradiographic analysis of ORN bone. These mechanisms are progressive macrophage-mediated osteoclast loss with no accompanying

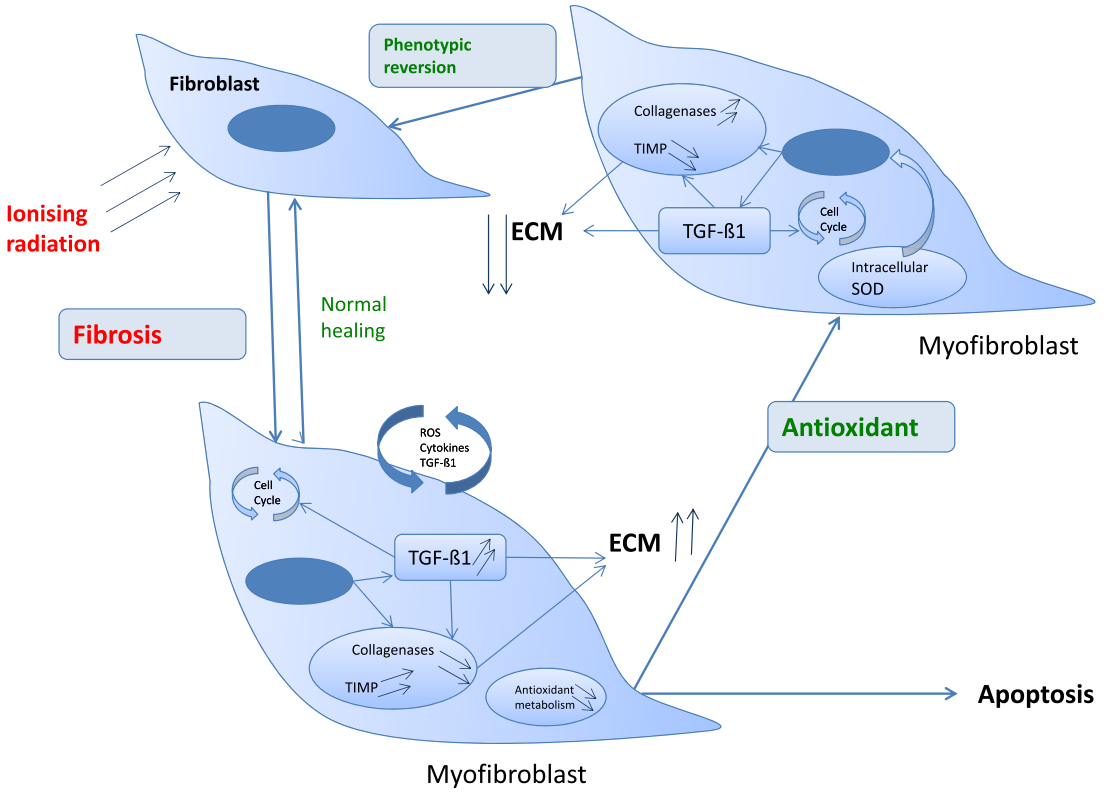

Fig. 1. Activation and dysregulation of fibroblast activity. (*Modified from* Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. Radiother Oncol 2004;73(2):119–31.)