Pentoxifylline, tocopherol, and clodronate for the treatment of mandibular osteoradionecrosis: a systematic review

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Objective. The purpose of this study was to evaluate the healing benefit provided by the antioxidant and antifibrotic properties of pentoxifylline–tocopherol or pentoxifylline–tocopherol–clodronate in combination therapy for osteoradionecrosis.

Study Design. We searched for relevant reports in PubMed by using a combination of "osteoradionecrosis" and the following keywords: "pentoxifillyne," "tocopherol," "vitamin E," or "clodronate." We considered articles in English or Spanish, with no limitations on the publication date.

Results. The combination of pentoxifylline plus tocopherol with or without clodronate was found to be effective for the treatment of mandibular osteoradionecrosis, although data were generally scarce and mostly came from retrospective case series.

Conclusions. This drug therapy is well tolerated and could be promising for the treatment of mandibular osteoradionecrosis, but prospective randomized controlled clinical trials are needed for further clarification. (Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:431–439)

Mandibular osteoradionecrosis (ORN) is a rare but complex, multifactorial complication of some head and neck tumors treated with radiotherapy (RT). In 1926, Ewing, as described by Jacobson et al.,[1] was the first to detect bone changes associated with this therapy, and Ewing termed these changes "radiation osteitis." ORN is characterized by bone exposure in an area that was previously irradiated for more than 3 months, with no evidence of healing, and resulting in necrosis of the surrounding soft tissues in a variable manner, in the absence of local neoplastic recurrence or metastatic disease.[2,3] Its incidence ranges from 0.4% to 56%, and dental extraction is the main risk factor,[4,5] although it can also occur spontaneously after radiotherapy doses exceeding 50 to 60 Gy (Table I[6-13]). The mean age at onset is 50 years,[6,9,14] and the male/female ratio in people affected is 1.6:1.[15] Bone absorbs 6 times more radiation compared with soft tissue[16,17] and is thus more vulnerable to radiation side effects. The mandible is the most affected area because it receives a higher dose of radiation and has a higher bone density than the maxilla.[18] Within the mandible, the most affected areas are the angle and the body because their blood supply is exclusively provided by the inferior alveolar artery, which makes these areas more dependent on the periosteum.[19,20] Most cases develop during the first 3 years (70%–94%), with a peak between 6 months and 2 years after completion of radiotherapy,[11] although risk of developing this pathology can persist for many years.[7,10,20] Once established, the wound does not heal spontaneously and can remain stable or deteriorate gradually, with periods of acute inflammation.[21] Diagnosis and classification are based on clinical and radiologic features, which are not apparent until 3 to 6 months after the onset of the clinical symptoms.[2] In addition, these criteria are only met if the degree of demineralization reaches 30% to 50%.[12] Currently, there are no effective radiologic tests for early diagnosis; computed tomography (CT) is the technique that most accurately correlates radiologic findings and clinical extension. Nevertheless, orthopantomography is sufficient to support therapeutic decisions in the early stages, although this approach may underestimate the extent of the disease.[22]

The underlying mechanisms of these radiation-induced injuries remain unknown. Watson and Scarborough[23] were the first to suggest local trauma and infection as possible causes of ORN, a theory later expanded by Meyer[24] in 1970. In 1983, Marx[2] proposed the "three H" theory (hypoxia–hypocellularity–hypovascularism). He observed that ORN is not a primary infection of the irradiated bone but that metabolic and homeostatic tissue

Statement of Clinical Relevance

Mandibular osteoradionecrosis continues to be one of the most problematic and severe complications of head and neck radiotherapy. There is ongoing controversy about the ideal therapy for this condition.

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Table I. Risk factors associated with osteoradionecrosis

Factors related to the tumor	- Tumor stage (>T1)[6] (*) - Tumor size[6] (*) - Bone invasion or proximity[7]
Factors related to the treatment	- Mandibular osteotomy[4] - Neoadjuvant RT and/or followed by surgery[8,9] - RT dosage >60 Gy[4] - Short RT regimens with high doses per fraction (>1.8 Gy)[10] - Brachytherapy[10] - QT combined with RT[10] (*)
Factors related to the patient	- Chronic pathologic local condition (periodontal disease)[10] (*) - Pre-RT dental health[10] (*) - Poor prosthetic adjustment[10] - Intraoral local trauma and/or biopsy[4,5] - Dental extractions pre-RT (<21 days) or post-RT (<2 years)[2,10,11] (*) - Smoking and alcohol consumption[12] (*) - Diabetes mellitus[13] (*) - Hypertension[13] - Malnutrition[13] - Inmunodeficiency[13] - Connective tissue disorders[13]

RT, radiation therapy; *QT*, chemotherapy.
*In addition to being causal risk factors, they have been related to its severity.[4,5]

alterations cause cell death as a result of persistent hypoxia and chronic injury. The increase in the cells' basal metabolism creates a stress that prevents the tissue from repairing itself.[2,25] In 2004, this theory was questioned by Delanian and Lefaix,[21] who suggested that trabecular bone is devitalized by radiation-induced endothelial damage, either directly or indirect via several harmful events triggered by reactive oxygen species: constant release of cytokines fibroblasts, excessive myofibroblast proliferation, and release of abnormal extracellular matrix components, which may not be removed because of defective retroregulation.[21] Such an imbalance between tissue synthesis and degradation generates progressive hyalinization and fibrosis of the medullary spaces,[26] which, in turn, cause bone hypovascularization and development of radiation-induced fibrotic (RIF) scar tissue.[21] Although this damage was traditionally considered irreversible, Delanian and Lefaix[21] suggested that the process could actually be reversed by antioxidant therapy with pentoxifylline, tocopherol, and clodronate.

Pentoxifylline is a methylxanthine derivative that exerts an anti–tumor necrosis factor-α effect, increases erythrocyte flexibility, produces vasodilation, and inhibits inflammatory reactions in vivo. In vitro, it has been shown to cause reduced fibroblast proliferation and increased collagenase activity. Tocopherol refers to several organic compounds that act as vitamin E. These compounds have antioxidant properties that help protect cell membranes against lipid peroxidation and partial inhibition of transforming growth factor-β_1, as well as vitamin K antagonistic properties that may induce changes in coagulation.[27] Clodronate is a first-generation, nonnitrogenous oral bisphosphonate, which is not associated with drug-induced osteonecrosis,[27-29] and can reduce osteoclast activity, decrease fibroblast and macrophage proliferation,[30] and promote bone formation by osteoblasts.[31] To date, pentoxifylline has been used to treat RIF of soft tissue and, used in isolation, has been shown to reduce the healing time of superficial wounds.[32-34] Combining pentoxifylline with tocopherol (PVe) and clodronate (PENTOCLO) enhances its antifibrotic effect, making it more effective than placebo or any of these agents alone.[35]

There is ongoing controversy about the ideal therapy for this condition, but it is widely agreed that it must be multimodal. Conservative treatment based on strict oral hygiene, cessation of tobacco and alcohol consumption, use of fluoride gel and aqueous chlorhexidine rinses—alone or with analgesics—are all still essential in the initial stages of ORN and are effective in 25% to 44% of cases.[14,36,37] Whenever signs of bone devitalization are observed, a curettage or sequestrectomy is necessary. Photobiomodulation therapy or hyperbaric oxygen (HBO) therapy may also be performed. Although there is no current evidence that HBO cures mild or moderate ORN,[38,39] it is known to be useful for preventing late-onset radiation-induced tissue damage by improving mucosal healing, restoring bone continuity, and decreasing wound dehiscence.[40] It may also help improve or stabilize ORN-related symptoms, such as xerostomia, pain, erythema, and edema.[41,42] Despite these advantages, HBO therapy requires a considerable amount of equipment and is time consuming, causes claustrophobia in patients, and is expensive. Given these factors and current knowledge about the pathophysiology of ORN, medical treatment with antioxidant drugs is currently the most common first option.

The aim of this study was to perform a systematic literature review to evaluate current evidence on the effectiveness of the following drug combinations in treating mandibular osteoradionecrosis: pentoxifylline–tocopherol and pentoxifylline–tocopherol–clodronate.

MATERIALS AND METHODS

We adhered to the tenets of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. No approval by an institutional review board was necessary, given the nature of this study. We performed a detailed electronic database search (MEDLINE and PubMed, July 2017) using a combination of "osteoradionecrosis" and the following terms to identify relevant articles: "pentoxifillyne," "tocopherol," "vitamin E," or "clodronate." The review analyzed all articles available either in English or Spanish, with no limitations on the publication date. Reviews, duplicate