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PENTOXIFYLLINE AND TOCOPHEROL IN THE TREATMENT OF OSTEORADIONECROSIS OF JAW – AN UPDATE

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ABSTRACT

Osteoradionecrosis of jaw is one of the significant complications of radiotherapy in head and neck cancer patients. This article reviews pathophysiology and newer treatment options for osteoradionecrosis. Newer modalities of treatment include combination therapy of pentoxifylline and tocopherol for osteoradionecrosis. In this article basic information about pentoxifylline and tocopherol and recent reports of their clinical application in the treatment of osteoradionecrosis of jaw is reviewed. Literature Reports show that these drugs offer potentially curative therapy for osteoradionecrosis and requires further high quality clinical trial evaluation.

KEYWORDS: ***Pentoxifylline, Tocopherol, Radiotherapy, Osteoradionecrosis***

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INTRODUCTION

Radiotherapy is largely used for treatment of head and neck cancer, as primary therapy, adjuvant to surgery, in conjunction with concurrent chemotherapy or as palliative treatment for late stage and unresectable head and neck malignancies. Although the radiotherapy can increase cure rates, the irradiated patient is susceptible to secondary effects and a series of potential oro- facial complications. One of the worst complications is osteoradionecrosis [ORN], which alters form and function of the jaws and oral cavity resulting in deterioration of the patient's quality of life. Recently a new theory called 'fibro-atrophic' theory has been proposed for ORN by Delanian and Lefaix[1]. This lead to the trial and application of new drugs in the management of osteoradionecrosis. Pentoxifylline[2] which is mainly used in treating intermittent claudication acts against TNF. Tocopherol[2] scavenges free radicals generated during oxidative stress and protects cell membranes against lipid peroxidation. Combination of these two drugs proved to be synergestic anti-fibrotic agents. This article intends to provide current trends in medical management of ORN of jaw using pentoxifylline and tocopherol.

OSTEORADIONECROSIS

ORN is best defined as a slow-healing radiation-induced ischemic necrosis of bone , 3-6 months of duration with associated soft tissue necrosis of variable extent occurring in the absence of local primary tumor necrosis, recurrence, or metastatic disease. Symptoms can include pain, bad breath, dysgeusia, dysesthesia or anesthesia, trismus, difficulty with mastication, deglutition, and/or speech, fistula formation, pathologic fracture, and local, spreading, or systemic infection. ORN has overall incidence rate of 11%, common in dentate patient, mostly in the posterior mandible . A review of the available literature implicates the following candidate variables for development of ORN: total radiation dose, photon energy, brachytherapy, field size, fractionation, periodontitis, preirradiation bone surgery, poor oral hygiene, alcohol and tobacco use, dental extractions, tumor size, location, and stage, proximity of tumor to bone, lack of HBO therapy, increased time since radiation, lack of radiation shields, and edentulousness.

PATHOPHYSIOLOGY

Watson and scarborough[3] proposed that osteoradionecrosis occurs due to combination of radiation, trauma and infection. Later marx[4] described that radiation induces endarteritis leading to tissue hypoxia, hypocellularity and hypovascularity. Fibro-atrophic theory[1] is a new theory which says that after radiotherapy there is an alteration and dysregulation of fibroblastic activity,endothelial cell damage and vascular thrombosis which ultimately leads to necrosis of bone.Radiation-induced endothelial injury initiates cytokine release, including tumor necrosis factor alpha (TNF α); fibroblast growth factor b; platelet derived growth factor; interleukin (IL) 1, 2, and 4;connective tissue growth factor; and transforming growth factor b1 (TGF-b1). This process produces a predominance of the myofibroblast phenotype, with attendant high rates of cellular proliferation and release of abnormal extracellular matrix (ECM) components. These myofibroblasts also demonstrate impaired ability to breakdown the abnormal ECM[5].

TREATMENT OPTIONS

Treatment may vary from conservative to surgical approach depending upon the nature and severity of the condition. Saline irrigation, chlorhexidene mouth washes, antibiotics, hyperbaric oxygen therapy has been tried in the past. Recent understanding of the pathophysiology of osteoradionecrosis based on the concept of radiation-induced fibrosis have led to the advent of new therapeutic regimens composed of pentoxifylline and tocopherol.

PENTOXIFYLLINE

Pentoxifylline is a tri-substituted methylxanthine derivative chemically designated as 1-(5-oxohexyl)-3,7-dimethylxanthine, and is a hemorrheologic agent. Its chemical name is 3,7- dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione and its molecular formula is $C_{13}H_{18}N_4O_3$, with a molecular mass of 278.3. Pentoxifylline is a white to creamy white crystalline powder. It is freely soluble in chloroform and methanol, soluble in water, sparingly soluble in ethanol and toluene, and slightly soluble in ether. It has a melting point of 104 to 107 °C, within a 3°C range . Intake is through oral route,metabolized in liver and via erythrocytes, half-life of 0.4-0.6 hrs [1-1.6 hrs for active metabolite], and excretion via urine.

MECHANISM OF ACTION

Pentoxifylline is a competitive nonselective phosphodiesterase inhibitor, which raises intracellular cAMP, activates PKA, inhibits TNF and leukotriene synthesis, and reduces inflammation and innate immunity, improves red blood cell deformability (known as a haemorrheologic effect), reduces blood viscosity and decreases the potential for platelet aggregation and thrombus formation, and is also an antagonist at adenosine 2 receptors. Pentoxifylline exerts an anti-tumor necrosis factor (TNF)-α effect, increases erythrocyte flexibility, vasodilates, inhibits inflammatory reactions in vivo, inhibits human dermal fibroblast proliferation and ECM production, and increases collagenase activity in vitro[2]. Pentoxifylline and its metabolites improve blood flow by decreasing its viscosity. In patients with chronic peripheral arterial disease, this effect increases blood flow to the affected microcirculation and enhances tissue oxygenation and decreases fibrosis of tissues[6].

MEDICAL USES

Primary use is to treat symptoms of intermittent claudication resulting from peripheral artery disease. Others include radiation-induced fibrosis, multi-infarct dementia, sickle cell disease,peripheral neuropathy, sarcoidosis, endometriosis, peyronie's disease, alcoholic and non-alcoholic steatohepatitis[6,7,8].

DOSAGE

Extended-release tablet form is 400 mg, three times a day with meals. While the effect of pentoxifylline may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks[9]. Dose related central nervous system and digestive tract side effects may occur, if so it is advised to lower the dosage to one tablet bid,800 mg/day. If side effects persist at this lower dosage, the administration of pentoxifylline should be discontinued. After its oral administration in aqueous solution, it is almost completely absorbed. Peak plasma levels of the parent compound and its metabolites are reached within one hour. The major metabolites are metabolite I (1-[5-hydroxyhexyl]-3,7-dimethylxanthine) and metabolite V(1-[3-carboxypropyl]- 3,7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater than pentoxifylline, respectively[10.]

CONTRAINDICATIONS

Retinal or cerebral haemorrhage, Risk factors for haemorrhage [patients on warfarin therapy] Concomitant administration with theophylline containing drugs may lead to theophylline toxicity Reduces blood pressure in patients receiving concomitant anti-hypertensive therapy

TOCOPHEROL

Tocopherols are a class of organic chemical compounds consisting of various methylated phenols, many of which have vitamin E activity. It's vitamin activity was identified in 1936 as adietary fertility factor in rats and named"tocopherol" from the Greek words (tókos, birth) and (phérein,to bear or carry) meaning "to carry a pregnancy," with the ending "-ol" signifying its status as a chemical alcohol. Tochotrienols are related compounds that also have tocopherol activity. All of these derivatives with vitamin activity may correctly be referred to as "vitamin E". Tocotrienols have the same methyl structure in its ring and the same Greek letter-methyl- notation, but differ from tocopherols due to the presence of three double bonds in the hydrophobic side chain. Whereas tocopherols have three centers and

eight possible stereoisomers per structural formula, the unsaturation of tocotrienol tails has only a single stereoisomeric carbon and, thus, two possible isomers per structural formula, one of which occurs naturally.Vitamin E exists in eight different forms, four tocopherols and four tocotrienols. All feature a chromane ring, with a hydroxyl group that can donate a hydrogen atom to reduce free radicals and a hydrophobic side chain that allows for penetration into biological membranes. Each form has a different biological activity; the unnatural l-isomers of tocotrienols lack almost all vitamin activity, and half of the eight possible isomers of the tocopherols, those with 2S chirality at the ring-tail junction, also lack vitamin activity. Of the stereoisomers which retain activity, increasing methylation, especially full methylation to the alpha-form, increases vitamin activity.Both the tocopherols and tocotrienols occur in α, β, γ and δ forms,determined by the number and position of methyl groups on the chromanol ring.

FUNCTIONS

Tocopherols and tocotrienols are fat-soluble antioxidants, but also seem to have many other functions in the body. The functions of endogenous tocopherol are to scavenge the reactive oxygen species generated during oxidative stress that escape the activity of in vivo antioxidant enzymes, to protect cell membranes against lipid peroxidation, and to partly inhibit TGF-ß1 and procollagen gene expression, thus reduces fibrosis[11].DOSAGE Oral – 1000 I U / day

PENTOXIFYLLINE AND TOCOPHEROL COMBINATION THERAPY

Combination of pentoxifylline and tocopherol [PENTO] has been proven effective both in prevention and treatment of ORN by Delanian and Lefaix[2]. These drugs when used alone were unable to reverse the development of fibrosis. But when combined, they act synergetically and have potent anti-fibrotic action. With the emergence of fibro-atrophic theory[1] which explains the pathogenesis of ORN, this drug combination reduces fibroatrophic changes in tissues and enhances wound healing by stimulating defective osteoblasts. All patients having dental extractions could be given eight weeks of pentoxifylline 400 mg twice daily with tocopherol 1000 IU, starting a week before the procedure. If ORN develops, then they could be continued for a further 6 months with clodronate prescribed after 3 months if there has been no appreciable response. Delanian and Depondt[1] treated 18 patients with ORN using pentoxifylline and tocopherol, with (8 patients) and without (10 patients) the addition of clodronate. Complete healing of mandibular ORN was seen at 6 to 8 months for 89% of the total sample, irrespective of clodronate. Delanian et al[12]. in the context of prolonged treatment of 54 patients with oseoradionecrosis involving a pentoxifylline dose of 800 mg/day and vitamin E 1000 IU/day (5 days a week), recorded an 89% reduction in bone exposure after 12 months, and an even greater reduction over longer periods of treatment. S.Nabil, N.Samman[13] have also described the successful use of these drugs in treating ORN. In a retrospective series of 12 patients treated with PENTO McLeod and colleagues[14] show more modest treatment outcomes. These patients were treated for a mean of 14.8 months. The Bradford Teaching Hospitals series reports [15]on 18 patients with ORN after radiotherapy or chemoradiotherapy (McCaul and colleagues, unpublished data, 2014), who received prospectively PENTO regimen, ORN resolved in 7patients (44% of patients completing therapy); in 3 with medical therapy alone and in 3 with medical therapy and surgical debridement. Three patients received hyperbaric oxygen therapy as part of ORN management. In 1 patient, medical therapy resulted in a symptom-free fibrous bony union of the right body of the mandible. No adverse events have been associated with vitamin E and pentoxifylline therapy in the Bradford series. None of these patients have experienced progression on therapy, and none have required major resection and reconstruction for ORN in the past 8 years. Nora Kahenase *et al*[16]. presents a case of a 66-year-old man with unevoked ORN of the left posterior lingual mandibular cortex that was

successfully treated and resolved with 6 months of pentoxifylline 400 mg twice a day and tocopherol 1000 IU every day.Silvestre et al[17] have described the usefulness of PENTO in treating ORN._Delanian. S. *et al*[18-20] have conducted several research with PENTO regimen for treating ORN of jaw and has shown successful results. D'souza *et al*[21]have discussed ORN cases treated with PENTO and doxycycline regimen. They have observed good results and it also proves to be cost effective treatment. Huan fan *et al*[22] have given latest updates regarding clinical literature review on PENTO regimen and its effectiveness on ORN induced rat models. Epstein *et al* [23]have shown that bisphosphonate associated osteonecrosis can be treated with PENTO regimen.

CLODRONATE

This is a first-generation, nonnitrogenous bisphosphonate used in osteoporosis, hyperparathyroidism, hypercalcemia of malignancy, and multiple myeloma. Clodronate reduces bone resorption through reducing osteoclast numbers and activity and is also known to reduce inflammatory cytokines IL-1b, IL-6, and TNF-α. It also acts on osteoblasts to increase bone formation and reduce fibroblast proliferation. Pentoxifylline and tocopherol combined with clodronate named PENTOCLO has shown successful results in treating ORN. Delanian et al[24,25] have described 2 phase II trials of combined therapy for ORN of the mandible. In the first, 18 consecutive patients were treated with pentoxifylline and tocopherol. Each had at least 13.4 mm of exposed mandibular bone and all had been prescribed pentoxifylline, 400 mg twice daily and tocopherol, 1000 IU orally for 6 to 24 months. The worst affected cases were also given clodronate, 1600 mg daily for 5 days per week. The second trial, published in 2011[25], reported on 54 patients who received radiation for head and neck cancer a mean of 5 years before the onset of ORN. In this report, the term PENTOCLO was coined for the treatment regimen including all 3 agents. This treatment regimen had evolved to combined pentoxifylline and tocopherol as described earlier, with clodronate, 1600 mg given 5 days per week, and prednisone, 20 mg, with ciprofloxacin given on the other 2 days. This study showed that prolonged treatment was safe and well tolerated. All patients in the study experienced improvement, with an exponential progressive and significant reduction in exposed bone with complete recovery.

CONCLUSION

Pentoxifylline and tocopherol are drugs that are readily available, well tolerated, pain diminishing, safe and cost effective. PENTO with or without CLODRONATE has promising potential, both in prevention and treatment of osteoradionecrosis of jaw.

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