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Review Article

ORAL MUCOSITIS AND MELATONIN

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A B S T R A C T

Mucositis, one of the most severe toxic side effects of cancer therapy, can affect the entire gastrointestinal tract, with the oral cavity being the most common affected site. It presents in virtually all head and neck cancer patients receiving chemo and/or radiotherapy, in 60-85% of those receiving myeloablative therapy for stem-cell transplantation, and in 20-40% of patients receiving conventional chemotherapy. The use of concomitant chemotherapy and/or targeted agents increases the risk of mucositis. Oral lesions lead to considerably decreased quality of life in these patients due to solid and liquid food dysphagia, dysarthria, and odynophagia, resulting in depression in some patients, who often require percutaneous endoscopic gastrostomy tube insertion. In addition, mucositis lesions may represent a gateway for opportunistic infections, can complicate cancer treatment, and extend hospitalization. On the other hand, given its dose-limiting toxicity for both chemo and radiotherapy, mucositis can have a direct impact on survival rates. As ROS are involved in the manifestation of precancerous lesions such as leukoplakia and lichen planus, melatonin plays a preventative or therapeutic role against oral cancer due to its antioxidant properties. Additionally, melatonin prevents damage to healthy tissues due to radiotherapy, which is routinely employed to treat oral cancers. A recent in vitro study suggests that melatonin may impede metastasis of oral cancer by inhibiting metalloproteinase-9 activation. Therefore, oral rinses, gels, and toothpastes containing melatonin may be beneficial for impeding and preventing oral cancer.

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INTRODUCTION

Oral cavity cancer, predominantly oral squamous cell carcinoma (OSCC), is an important cancer, globally affecting 270,000 people worldwide each year[1].Despite of the recent progress in the diagnosisand therapy of OSCC, the 5-year survival rate has not improved in more than two decades[2].Therefore, a more comprehensive understanding of the molecular pathogenesis of OSCC is urgentlyneeded to identify new targets for the effective therapy and to recognize the early state of OSCC or,when it is possible, premalignant lesions. The development of OSCC has been reported as one of themost important complications of a chronic inflammatory disease of the oral mucosa[3],called orallichen planus (OLP)[4,5]even if in OLP patients the underlying mechanisms of malignant transformationhave not been clearly established. The association of chronic inflammation with a variety of cancers, including OSCC, has been amply addressed[6-8].ROS and RNS are considered to play a key role in inflammation-mediated carcinogenesis.

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ROS can generate DNA base alterations, strand breaks, damage to tumor suppressorgenes, and enhanced expression of proto-oncogenes[9]. ROS-induced mutation could also arise fromprotein damage and attack on lipids, which then initiate lipid peroxidation[10], resulting in the transformationof normal cells into malignant cells[11]. Any changes in enzymatic and nonenzymatic antioxidantdefense systems may break cellular equilibrium and cause damages and ultimately malignant transformation. In addition, overproduction of NO leads to generation of various RNS[12].

Excess of NO is produced from inflammatory cells via the expression of Inos[13,14]. Chronic inflammationinduced iNOS-dependent DNA damage in not only inflammatory cells but also epithelialcells, which could potentially develop into cancer[15,16]. Therefore, this DNA damage could possiblyimply an association between the existence of OLP and development into oral cancer. Moreover,the magnitude of the inflammation damage associated to carcinogenesis depends not only on ROS/RNS levels but also on the body's defense mechanisms, mediated by various cellular antioxidants.Disruption of this delicate oxidant/antioxidant balance in the body seems to play a causative rolein carcinogenesis[17]. Therefore, melatonin, which is a potent scavenger of the hydroxyl radical andperoxynitrate, may be useful in treating oxygen radical

pathophysiology[18]. Parallel to that, melatoninstimulates the activity of antioxidative enzymes and inhibits pro-oxidative enzymes, thusphysiologically synergizing with its direct free radical scavenging properties. For all these reasons,an inverse interaction between melatonin and carcinogenic processes is of focal importance[19].

Generally, OSCC is considered to arise through the progressive accumulation of multiple genetic abnormalities that impair the functions of oncogenes or tumor-suppressor genes[20]. Besides geneticalterations, evidence has emerged that the DNA methylation of 5′-CpG islands has been shown to bea major cause of inactivation of tumor-suppressor genes in human OSCC[21]. Melatonin receptor 1A(MTNR1A), which encodes for one of two high affinity forms of a melatonin receptor, seems to bea candidate target involved in the etiopathogenesis of OSCC. Interestingly, expression of this genewas frequently silenced in OSCC cell lines without its homozygous loss, although it was presentin normal oral mucosa, suggesting that MTNR1A might be inactivated epigenetically in OSCC andcontribute to oral carcinogenesis. In several cancers, indeed, it has been reported that melatonintreatment or ectopic expression of MTNR1A has a growth suppressive effect on cancer cells in vitroand in vivo[22,23] even though the intracellular mechanisms behind the antiproliferative actions ofmelatonin remain unclear.

Pathophysiology of Mucositis

Recent developments in mucositis research have highlighted multiple factors which contribute to mucosal injury[24] . A five-phase chronological process has been proposed: initiation, primary damage response (upregulation and message generation), signal amplification, ulceration, and the healing phase[25]. Mucositis commences when gastrointestinal (GI) mucosa are exposed to cytotoxic agents, resulting in cellular DNA damage and cell death, mainly through the generation of oxidative stress and reactive oxygen species (ROS) formation. ROS directly induce tissue injury and trigger a cascade of inflammatory pathways[26]. Ortiz et al. have also observed a mitochondrial oxidation response to radiation with subsequent mitochondrial dysfunction[27].

The progression of mucositis is characterized by significant inflammatory mediator up-regulation due to the activation of the NF-κB pathway (upregulation and message generation phase). This is followed by the signaling and amplification phase, during which, once activated by chemotherapy and ROS, NF-κB promotes the expression of multiple pro-inflammatory molecules, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), TNF-α, and pro-IL-1β, and ensures feedback amplification of the NF-κB-dependent signaling pathway[26] . Furthermore, mitochondrial ROS production promotes inflammation by activating a multi-protein cytoplasmic complex, such as the NLRP3 (NACHT, LRR, and PYD domains-containing protein3) inflammasome. NLRP3 inflammasome assembly leads to caspase-1 activation and subsequent cleavage of pro-cytokines such as pro-IL-1β, pro-IL-18, and pro-IL-33 into their mature form[27,28]resulting in ulceration (ulceration phase). Therefore, the NF-κB pathway, mitochondrial dysfunction, and subsequent NLRP3 inflammasome activation are the three main players involved in the development of oral mucositis, which amplify the whole inflammatory process via positive feedback loops, thus prolonging tissue injury and ending in the healing phase.

During the initiation phase of mucositis, patients begin to develop erythema followed by focal areas of oral mucosal desquamation[29], which mainly occur at the submucosa and basal epithelium level. Therefore, although no evident damage to mucosal integrity is observed clinically, the tissue biology is altered[26]. The progression of mucositis is then prolonged and severe, mucosal integrity is breached, ulceration begins to form and the patient starts to have a burning sensation. Atrophic changes occur in the GI mucosa, culminating in tissue injury and stem cell death. GI epithelial integrity and function are destroyed and impaired, respectively. A fibrinous exudate, or pseudomembrane, containing bacteria covers the ulcer. Bacterial colonization at the mucosa ulcers further induces inflammation by stimulating infiltration and activation of macrophages, which occurs approximately two weeks after therapy[26]. Cell wall residues originating from colonizing bacteria penetrate the submucosa, where they activate macrophages in the infiltrate[30]. This can lead to prolonged hospitalization, the need for parenteral nutrition, severe pain, risk of infection and sepsis, and increased risk of morbidity and mortality.

The final stage of mucositis pathobiology is the healing process. Epithelial cells controlled by signals secreted by the extracellular matrix, which are then downregulated to avoid hyperplasia, migrate, grow, and differentiate to form a wound. With the healing process under way, symptoms begin to abate[25], and healing is completed within 4 weeks after the final dose of radiation. Unfortunately, even after full replenishment of the epithelium, the structure of the reconstituted submucosa differs from its pre-radiotherapy state[31].

Mucositis Management

As there is no effective therapy for mucositis or its associated pain, a large number of studies have been conducted in this field. Strategies for managing oral mucositis include preventative measures and therapeutic approaches[29] (Figure 1).

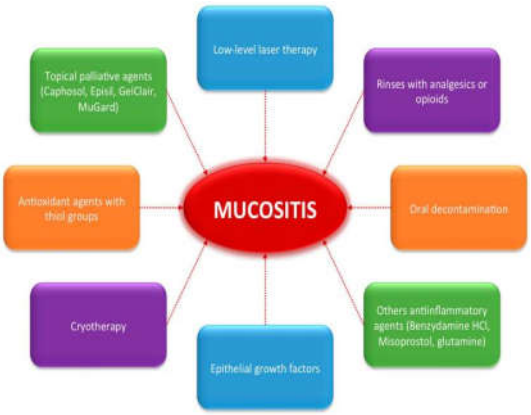

Figure 1 mucositis management

Melatonin: A New Treatment for Mucositis

Melatonin (*N*-acetyl-5-methoxytryptamine), a hormone synthesized from tryptophan, is produced by the pineal gland; it has been detected in multiple extrapineal organ tissues at much higher concentrations than in the pineal gland[32] . It is a potent free radical scavenger with anti-oxidant properties , which increases the expression and activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione reductase (GRd), and γ-glutamyl-cystein synthase. This special class of antioxidant generates a series of metabolites that are also free

radical scavengers when scavenging free radicals[33-37] . In other words, as compared to other antioxidants, melatonin is more effective in preventing damage caused by oxidative stress. Capable of crossing cell membranes and of easily reaching all cell compartments, it is taken up by mitochondria and can maintain mitochondrial homeostasis in different experimental models[32,38-41]. Melatonin increases membrane fluidity, electron transfer chain (ETC) complex activity, ATP production, and mitochondrial membrane potential, while reducing oxidative stress and closing mitochondrial permeability transition pores (MPTPs)[42]. Its important anti-inflammatory effects include expression inhibition of iNOS/i-mtNOS, COX-2, and pro-inflammatory cytokines such as IL-1β or TNF-α. Many of these properties are attributed to the inhibition of NF-κB-dependent innate immune pathway activation[43,44], and we recently showed that melatonin blunts NLRP3 inflammasome activation under different experimental conditions[27,45,46].

The therapeutic benefits of melatonin gel in combating oral mucositis (Figure 2).

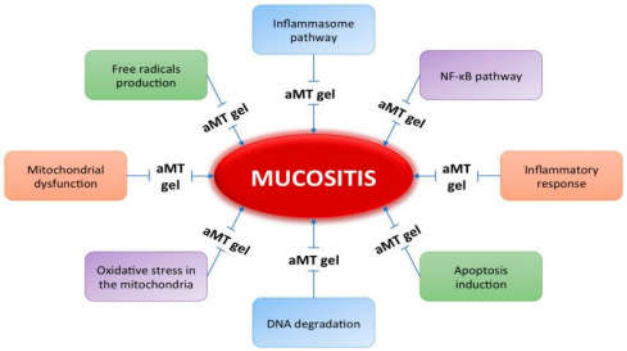

Figure 2 Therapeutic benefits of melatonin

Melatonin in Treatment of Oral Mucositis, a Complication of Chemotherapy

Oral mucositis is a consequence of the toxic effects of chemotherapeutic agents and irradiation on oral mucosa cells[47-49]. It is estimated that oral mucositis is a complication in 40% of patients receiving chemotherapy, more than 90% of those irradiated for head and neck cancer. This condition is frequently associated with severe pain and inflammation and can cause malnutrition, systemic infections, and low quality of life, as well as limiting chemotherapy doses. The clinical appearance of oral mucositis may range from mild discomfort and erythema to painful erythema and edema and/or ulcerations[50].The pathophysiology of mucositis is not known in detail. A complex hypothesis has been proposedto elucidate the mechanism by which mucositis develops and resolves. According to this,mucositis is a complex process, divided into four phases: an initial inflammatory/vascular phase, anepithelial phase, an ulcerative/bacteriological phase, and a healing phase[47]. The hypothesis speculateson the importance of the inflammatory response induced in the involved tissues by chemotherapyand ionizing radiation that occurs through the activation of intracellular and intercellularsignaling pathways, regulating gene expression of specific proteins involved in immune and inflammatoryprocesses (e.g., cytokines, adhesion molecules)[51,52]. Of the many drugs and methods usedto treat mucositis, none has been shown to be uniformly effective. Trials investigating locally andsystemically applied treatments of mucositis include immunomodulatory drugs, anticholinergicdrugs, cytokines, antiviral drugs, glutamine, and antioxidants.

Among the antioxidants currently under investigation, the pineal hormone melatonin could be added, as it has been claimed to have activity in the prevention of mucositis[53,54]. Locally and systemically applied melatonin has been shown to prevent and treat mucositis in patients with cancer[55]. The pineal hormone melatonin inhibits the production of free radicals that mediate the toxicityof chemotherapy. Nevertheless, experimental data are still controversial: chemotherapy-inducedstomatitis was not reduced in a study with the use of melatonin, although other toxic effects weredecreased[56-58]. Additional basic and clinical researches are needed to determine whether melatonincan be used to treat chemotherapy-induced mucositis.

CONCLUSIONS

In summary, oral mucositis is a clinically important, deleterious consequence of chemo and radiotherapy, for which no effective treatment has been found to date. Mucositis lesions can be painful, affect nutrition and quality of life, and have a significant economic impact. The pathogenesis of oral mucositis is multifactorial and complex, and not all mucositis can be prevented. Once mucositis has developed, therapy should focus on supportive care, which aims to maintain hydration, provide appropriate caloric intake through enteral or parenteral nutritional support, relieve pain, and to prevent infection. This review discusses current clinical practices in the management of oral mucositis and emphasizes that no standard therapeutic approach has been developed for patients suffering from oral mucositis. Thus, basic, translational, and clinical research into how to prevent and treat oral and gastrointestinal mucositis continues. Our findings, showing that melatonin reduces irradiation toxicity and prevents treatment-induced mucositis, indicate that, with its oncostatic and cytoprotective properties, it constitutes an innovative, adjuvant strategy in the treatment of cancer. We demonstrated that treatment with melatonin gel protects rats from post-radiation oral mucositis, prevents duodenal inflammation and necrosis, and restores mucosal endogenous melatonin levels in irradiated animals. A clinical trial of this gel, which is under patent, is currently underway to test for the prevention of oral mucositis in head and neck cancer patients.

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