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A Therapeutic Approach for Radiotherapy induced mucositis in Head and Neck Cancer Patients.

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ABSTRACT -
Modern advances in the field of medico-dentistry has caused formulation of innovative solutions. Many cancer patients undergoing systemic chemotherapy or radiotherapy or a combination of both, especially in head and neck region, are inherently prone to develop a frequent complication Recent years have also seen a considerable emphasis on growth factors, which has led to the recognition that they might have potential in the therapeutic management of these complications, either by regeneration through biomimetic or mimicking the processes that occur during embryonic and post-natal development. This review attempts to highlight the role of growth factors in the management of oral mucositis.

KEYWORDS
epidermal growth factor, keratiocyte growth factor, cancer, oral mucositis.

INTRODUCTION

Oral mucositis (OM) is described as inflammation of the mucosa in the oral cavity which is caused by destruction of the oral mucosal epithelial cells and growth suppression secondary to cancer treatment in the form of radiotherapy or chemotherapeutic drug substances Although it is less common, OM also can occur secondary to chemotherapy of various solid tumours. It is the most debilitating condition and the most common complication in cancer patients. Typical manifestations are atrophy, erythema, ulceration and swelling of the mucosa. It appears first by thinning of oral tissues which leads to erythema. As these tissues become thinner, ulceration eventually occurs. Potential complications include pain, increased risk of local and systemic infections, bleeding, insufficient food intake and may lead to breaks in treatment sessions. Oral mucositis along with xerostomia is one of the most common and a serious complication of anti-neoplastic therapy and occurs with a prevalence of approximately 40% in standard anti-cancer therapies[(1)]. The term “mucositis” was introduced in late 1980 to describe inflammation of the oral mucosa induced by radiotherapy (RT), chemotherapy (CT), and bone marrow transplantation and is said to be a manifestation of leukopenia[(2),(3)] . It generally presents shortly after the initiation of treatment and resolves usually within a week. The diagnosis of oral mucositis is according to clinical parameters and is manifested as pain, erythema, and ulcerations[(4)].

Oral mucositis that is induced owing to radiation therapy initially manifests as mucosal whitening even before the appearance of erythema and ulceration, and the lesions which are not in the field of RT may be due to candidiasis or

reactivation of herpes simplex virus. In contrast, CT oral mucositis presents bilaterally. As CT induces myelosuppression, there is an increased risk of systemic infection. The healing of oral tissues due to mucositis following RT takes 3 to 5 weeks, whereas, in CT-induced oral mucositis, the healing typically occurs in 2 to 3 weeks[5],[7].

Preventive and Therapeutic Approaches for Oral Mucositis Avariety of agents have been used for the prevention and management of oral mucositis either in topical form or systemically and are mentioned below[8],[10].

I. TOPICAL PHARMACOLOGICAL AGENTS

a. Antimicrobial agents
b. Antiseptic agents
c. Anti-inflammatory agents
d. Mucosal protectants
e. Local anesthetic agents
f. Episil (Combination of phospholipids and glycerol dioleate)
g. Gelclair (Hyaluronic acid)
h. Matrix metalloproteases blockers

II. SYSTEMIC PHARMACOLOGICALAGENTS

a. Antioxidants
b. Antifungal agent
c. Growth factors
d. Stem cell therapy

III. ALTERNATIVE AGENTS

a. Honey
b. Capsaicin
c. Chamomile
d. Coffee
e. Propolis
f. Ozonated water

IV. MISCELLANEOUS

a. Oral care protocol
b. Cryotherapy
c. Radiation shields
d. Low-level laser therapy

GROWTH FACTORS

"Growth factors are proteins that stimulate cellular growth, proliferation, and differentiation." Growth factors and cytokines bind to specific receptors on the cell membrane of target cells[11]. Growth factors are important as they have the capability of affecting a variety of cellular processes, which are important for the regeneration of tissues. Additionally, the self-healing capacity of the patients can be augmented by the use of growth factors[12]. They also alter the complex balance of pro and anti-inflammatory cytokines involved in the pathogenesis of oral mucositis[11],[13].Currently, growth factors are recommended in the prevention of oral mucositis in hematological cancers undergoing high-dose CTand total body irradiation prior to hematopoietic stem cell transplantation[11].

Keratinocyte growth factor

Recent years have seen a breakthrough in the management of mucositis with the discovery of keratinocyte growth factor; this naturally occurring 28 KDA heparin binding member of the fibroblast growth factor family is capable of binding to its receptor on a variety of epithelial tissues inclusive of oral and gastrointestinal epithelial cells, keratinocytes on skin, stratified squamous epithelial cells hepatocytes, and type 2 pneumocytes[14]. Endogenous KGF is a potent epithelial mitogen, which is upregulated by the action of platelet-derived growth factor BB and TNF-α[15].

Palifermin

Palifermin is the first agent approved by FDA for its use in prevention and treatment of oral mucositis in hematological malignancies which is known to have several biological actions, which target multiple stages in the progression of oral mucositis[15]. Palifermin causes proliferation, differentiation, and migration of epithelial cells of tongue and buccal mucosa and increases the epithelial thickening of the squamous epithelium of the oral cavity[16].

Payandeh M,et al. carried out a meta-analysis of 10 studies from 2007 to 2015 on the efficacy of palifermin in oral mucositis and acute Graft Versus Host Disease (GVHD) after hematopoietic stem cell transplant in hematological malignancies and concluded palifermin to be associated with a reduction in the incidence and severity of oral mucositis, whereas no effect was seen in a GVHD[17].

Le Q, et al. compared palifermin (180 µg/mg) with placebo in a total of 188 head and neck cancer (HNC) patients (94 patients in each group) receiving conventionally fractioned RT (2.0 Gy/day for 5 days per week to 70 Gy) along with cisplatin (100 mg/m on days 1, 22, and 93). Which concluded that palifermin reduced the incidence of severe oral mucositis in patients receiving chemoradiotherapy for Head and neck cancer HNC. Further, it also delayed the development and shortened the duration of oral mucositis providing less use of an opioid analgesic[18]. Similar results were observed in another study conducted by Henke M, et al. in which palifermin was administered at a dose of 120 µg/kg once weekly in HNC patients undergoing postoperative chemoradiotherapy. They observed decrease severity of oral mucositis[19].

According to the reviewed literature, the administration of palifermin at doses between 1 and180 µg/kg/day reduces the incidence and severity of oral mucositis. The most frequent adverse reactions affect particularly the skin and oral mucosa, with dysgeusia, paresthesia, hypertrophy of the oral mucosa and tongue papillae; color changes of the oral mucosa, rash, pruritus, erythema, and hyperpigmentation of the skin, among other alterations[20].

Epidermal growth factor

Considered as a marker of mucosal damage, EGF is an important polypeptide which helps in epithelial cell proliferation, growth, and migration, thereby maintaining the tissue homeostasis[21].

Girdler NM conducted A phase I clinical trial on EGF mouthwash and concluded that it does not accelerate ulcer healing, but it may have the potential to protect the oral epithelium from cytotoxic damages[22].

Hong J,et al. in 2009 conducted a study in patients who were undergoing definitive RT of the head and neck region with or without combined CT developed oral mucositis these patients were administered topical rEGF for 7 days twice daily. Their results concluded the effectiveness and safety of rEGF in radiation-induced oral mucositis[23].

In contrast, a phase 2 clinical trial was conducted by Kim J,et al. in the year 2017 on the efficacy and safety of topical recombinant human epidermal growth factor (rhEGF) in oral mucositis induced by CT with hematopoietic stem cell transplantation. They used rhEGF in the form of oral spray and did not find any evidence for its role in reducing the incidence of oral mucositis[24],[25].

Transforming growth factor-β

A human recombinant form of TGF- β3 was shown to inhibit reversibly, the cycling of the epithelium, including human buccal mucosa. This polypeptide exerts an anti-proliferative effect on the epithelial and endothelial cells. It also reduces mucositis by arresting the mitosis of epithelial cells in the G1 phase and initiating the regeneration of clonogenic stem

cells. It showed a reduction in the severity of oral mucositis when applied topically in patients who received 5-fluorouracil[26],[27].

Colony-stimulating factors

Granulocyte colony-stimulating factor (G-CSF) and granulocytemacrophage colony stimulating factor (GM-CSF) were the first group of growth factors to have been tried in oral mucositis. These are the hematopoietic growth factors needed for the bone marrow progenitor cells to form mature blood cells. The CSFs are the G-CSF and GMCSF. G-CSF stimulates the development of neutrophils, eosinophils, and basophils, whereas the GM-CSF stimulates the generation of cells belonging to the monocyte/macrophage lineage. Both the factors enhance the functioning of peripheral neutrophils including those in mucosal tissues. The rationale behind numerous clinical trials on GCSF and GM-CSF can be attributed to its direct action on the peripheral neutrophils, thereby reducing neutropenia induced during CT, hence decreasing the infection and oral mucositis[28].

Patni N,et al. evaluated the response of GM-CSF (100 mcg per day subcutaneously) in radiation-induced mucositis in a total of 33 patients with stage I and II head and neck squamous cell carcinoma. Treatment with GM-CSF was initiated only when patchy fibrinous mucositis was observed, pain not responding to step 1 pain killers (WHO step ladder), and when difficulty in swallowing semisolid food was present. They concluded a decrease in the severity of oral mucositis, dysphagia, and reduced pain not requiring the use of opioid analgesics. Minimal side effects were observed and 2 patients out of 33 reported itching and erythema at the site of injection[29].

CONCLUSION

Prevention is essential part especially with the approach of addressing the treatment of the underlying oral disease and improve oral hygiene. Today, there are pharmacologic and non-pharmacologic methods for treating mucositis, particularly a combination of these methods together which can create greater therapeutic effects. Hoping more drug effectiveness of these methods on pain reduction, nutrition improvement . Oral mucositis is the most significant dose – limiting step in the cancer treatments and is associated with adverse effects. Reducing the morbidity of mucositis will help to avoid unwanted dose reductions or unscheduled breaks in cancer therapy and thus improve outcomes of cancer therapy. Till date, there is no effective gold standard treatment for oral mucositis. Literature has several good experimental evidencesto support the use of growth factorsin treating oral mucositis. Future research for the newer drugsin the field of radiation-induced oral mucositis is a must, and the current management should focus more on palliative measures, such as pain management, nutritional support, and maintenance,of good oral hygiene.

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