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Original Paper

Local Use of GM-CSF for Severe Mucositis

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INTRODUCTION

Ulcerative oral mucositis is a common side-effect of many forms of cancer chemotherapy and has an overall frequency of approximately 40% [1]. Oral mucositis causes discomfort, pain and interferes with oral nutrition. Mucositis can be a potential source of infection. Severe mucositis may lead to interruption of planned course of chemotherapy.

Two major mechanisms lead to oral mucositis: direct stomatotoxicity due to rapid cell turnover (7–14 days) in the upper digestive tract and indirect stomatotoxicity due to myelotoxicity and subsequent infections with bacteria (common isolated organisms include *Pseudomonas*, *Klebsiella*, *Escherichia coli*, *Serratia*, *Proteus*, *Enterobacter*, *Staphylococcus*, *Streptococcus*) [2], viruses (*Herpes simplex*, *Varicella zoster*) and fungi (*Candida albicans*) [3]. Factors that influence the frequency and severity of these complications may be grouped into those that are related to the cytotoxic treatment and those that are related to the patient. Cytotoxic treatment-depending factors are dose, schedule, regimen and drugs [4–7]. A wide variety of cytotoxic agents, like alkylants, antimetabolites, antibiotics, vinca alkaloids and biologics, may produce direct stomatotoxicity (Table 1). Patient-related factors include the types of malignancy (patients with haematological malignancies develop oral problems at two or three times the rate of patients with solid tumours) [4, 8, 9], patient age (young patients tend to develop oral problems more frequently than older patients) [1], and the level of oral health before and during therapy (patients with pre-existing peridontal disease, pulpal disease, irritating prostheses, sharp or broken teeth have a higher risk of developing oral infection) [10–14].

PREVENTION AND TREATMENT OF STOMATITIS

Pretreatment strategies to prevent and decrease the incidence of oral complications include a baseline oral assessment, treatment of pre-existing dental disease and patient education. Patients should be instructed to avoid the use of irritating or abrasive substances such as commercial toothpastes and mouthwashes, tobacco, alcoholic beverages, very spicy food, acidic food such as citrus fruits and their juices, and foods that are hard and coarse such as crackers or hard bread.

Normal saline or sodium bicarbonate solution are commonly suggested to enhance removal of debris. The effectiveness of hydrogen peroxide rinses is inconsistent; they break down granulating tissue and have an unpleasant taste [15]. Chlorhexidine mouthwash has been used prophylactically with significant reductions in patients undergoing bone marrow transplantation and who are at high-risk for oral infections [16]. The value of prophylactic antifungal agents is controversial [17–21]. These agents may not prevent mucositis, but they can assist in maintaining integrity of mucosa.

Cryotherapy reportedly has been helpful in marginally reducing the severity of chemotherapy-induced mucositis due to reduction of mucosal blood flow during chemotherapy administration [22]. Additional controlled trials are required to confirm this observation. The use of allopurinol, an inhibitor of orotidine-5′-phosphate decarboxylase, to prevent mucositis induced by 5-fluorouracil (5-FU) is unclear. Although two pilot studies suggested its efficacy, a larger controlled investigation failed to substantiate its usefulness [23, 24].

Sucralphate is a poorly absorbed basic aluminium salt of a sulphated disaccharide that is commonly used for the treatment of peptic ulcer disease. It forms a paste-like adhesive barrier that appears to protect against subsequent mucosal damage. Understandably, there has been interest in studying whether this drug prevents chemotherapy-induced mucositis. One small double-blind placebo-controlled clinical trial suggested that sucralphate reduced the incidence of mucositis caused by cisplatin/5-FU chemotherapy [25].

A relatively small placebo-controlled randomised study involving 34 patients evaluated the prophylactic use of acyclovir in patients receiving mucositis-producing chemotherapy for head and neck cancers [26]. This trial failed to show any suggestion of benefit from acyclovir in this situation. Mouthwashes with prostglandin E2-gel may lead to a reduction of pain and to a fast re-epithelialisation of chemotherapeutic destroyed oral mucosa [27]. A number of other compounds have also been proposed for the prevention of chemotherapy-induced mucositis, although none has been definitively evaluated. Included in this list are vitamin E [28], chamomile [15], and pentoxifylline [29].

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Table 1. *Oral mucositis causative cytotoxic agents*

Alkylating agents	Antibiotics
Nitrogen mustard	Bleomycin
Cyclophosphamide	Doxorubicin
Ifosfamide	Daunomycin
Procarbazine	Mithramycin
Antimetabolites	Vinca alkaloids
Methotrexate	Vincristine
Fluorouracil	Vinblastine
Cytosine arabinoside	Biologics
Mercaptopurine	IL-2
Hydroxyurea	IFN-α

Treatment with topical oral anaesthetics, such as viscous xylocaine, can relieve pain and help to maintain adequate oral intake. Xylocaine is often used alone or as part of a cocktail (containing other drugs, e.g. magnesium hydroxide, diphenhydramine and/or sucralphate). Also, benzocaine in a hydroxypropylcellulose base, an agent that produces a protective physical barrier, has been reported to be helpful [30].

At times, chemotherapy-induced mucositis may be severe enough to require hospitalisation. In this situation, narcotic analgesics may be needed for pain control and intravenous (i.v.) fluids may be necessary for hydration. Usually, mucositis resolves after a few days of supportive care.

Preliminary data suggest that some growth factors (e.g. granulocyte-macrophage colony-stimulating factor, GM-CSF) may have been positive modifiers of mucositis induced in myelosuppressed or radiated cancer patients [31]. The possible rationale for topical and systemic use of GM-CSF in cutaneous and mucosal lesions is the following [32, 33]: GM-CSF is a multilineage colony stimulating factor capable of stimulating early myeloid progenitor cells that differentiate into fully committed cell types. GM-CSF preferentially stimulates granulocytes and macrophages. It also stimulates various functional activities of monocytes and granulocytes. Macrophages are stimulated to secrete plasminogen activator. They also exhibit increased phagocytotic and cytocidal activity for bacteria and yeast and malignant cell lines. Granulocytes increase RNA- and protein synthesis and exhibit antibody-dependent autotoxic killing of tumour cells and enhance oxidative metabolism. GM-CSF stimulates neutrophils and eosinophils to augment surface antigenic expression and prolongs their survival. In addition, increases in phagocytotic activity, synthesis of biologically active molecules, antibody dependent cytotoxicity and expression of various cell surface markers have been noted [33].

Systemic treatment with GM-CSF of severe oral mucositis

Ausili-Cefaro and colleagues [34] initiated a comparison between rhGM-CSF and rhG-CSF administered during radiotherapy and after prolonged carboplatin infusion in preventing leucopenia and mucositis produced by chemoradiotherapy in advanced head and neck cancer. 5 patients received G-CSF and 6 patients received GM-CSF, both at a dose of 3 μg/kg/day subcutaneously (s.c.) for a duration of 14 days. These preliminary data showed that both GM-CSF and G-CSF slightly reduced the severity of leucopenia, but GM-CSF delayed the nadir mean day. Moreover GM-CSF given during radiotherapy remarkably reduced the severity of mucositis in comparison both with G-CSF and a historical group (Table 2).

Chi and colleagues [35] evaluated prospectively the effect of GM-CSF on oral mucositis in 20 head and neck cancer patients after cisplatin, 5-FU and leucovorin chemotherapy. After chemotherapy, GM-CSF (4 μg/kg s.c. from days 5–14) or no therapy was given by a randomised self-controlled crossover study design. The authors concluded that GM-CSF significantly reduced the severity and duration of chemotherapy-induced oral mucositis.

The efficacy and safety of GM-CSF on the frequency and severity of radiation-induced mucositis in patients with head and neck carcinoma was proven by Kannan and colleagues [36]. GM-CSF was given s.c. (1 μg/kg body weight daily) after radiotherapy with 20 Gy until the completion of radiotherapy. GM-CSF administration concurrently with conventional fractionated radiotherapy was feasible without significant toxicity and acute side-effects of radiotherapy namely mucositis, pain, and functional impairment were negligible or minimal. These results were suggestive of mucosal protection by GM-CSF during radiotherapy.

Topical treatment with GM-CSF of severe oral mucositis

Ovilla and colleagues [37] included in their trial two groups of 10 bone marrow transplantation patients each, with one of the groups using the GM-CSF mouthwashes once a day (400 μg of GM-CSF diluted in 100 ml of drinking water, later swallowed) as soon as symptoms of mucositis began. The authors concluded that the re-establishment of cell cycle improved the state of mucosa and symptoms due to a cascade

Table 2. *Topical or systemic GM-CSF for prevention and treatment of chemotherapy- and/or radiotherapy-induced oral mucositis*

Disease	Treatment	*n* patients	GM-CSF use	Results	Author [Ref.]
Head and neck	Radiochemotherapy	11	Systemic	Reduces the severity of mucositis	Ausili [34]
Head and neck	Chemotherapy	20	Systemic	Reduces the severity and duration of mucositis	Chi [35]
Head and neck	Radiotherapy	—	Systemic	Mucosal protection during radiotherapy	Kannen [36]
Various neoplasms	Bone marrow transplantation	10	Topical	Improvement in healing of mucositis	Ovilla [37]
Breast cancer	Chemotherapy	45	Topical	No effect	Cartee [38]
Various neoplasms	Chemotherapy	24	Topical	Reduces the severity and duration of mucositis	Haus [39]
AIDS, NHL	Radiotherapy	2	Topical	Improve acute mucosal toxicity	De La Torre [40]
Various neoplasms	Chemotherapy	14	Topical	Reduces the duration of mucositis	Cinat [41]
Various neoplasms	Chemotherapy	40	Topical	Reduces the severity and duration of mucositis	Ibrahim [42]

effect started locally by GM-CSF which released several peptide growth factors provoking chemotaxis of inflammatory cells involved in all stages of wound healing (Table 2).

Cartee and colleagues [38], conducted a double-blind, placebo-controlled, dose-ranging study of GM-CSF mouthwash in patients with breast cancer during the first treatment cycle of a combination chemotherapy regimen (5-FU, doxorubicin, methotrexate) which has historically produced dose-limiting (grade ≥ 3) mucositis in approximately 39% of patients. Subjects were randomised to receive either placebo mouthwash (0.1% albumin) or one of four concentrations of GM-CSF mouthwash (0.01, 0.1, 1.0 or 10 μg/ml). Solutions were administered four times daily starting within 24 h of chemotherapy initiation and continuing until the end of cycle (day 21). The incidence of grade 3 mucositis on day 15 was 38% (17/45) among all evaluable patients in this mouthwash study and 42% (15/36) among the subset of patients receiving GM-CSF. Logistic regression analysis of the 45 evaluable patients indicated a flat dose–response curve. Only 22% of the patients in the placebo group experienced grade 3 mucositis on day 15. Patients in the high-dose GM-CSF groups (1.0 μg/ml and 10 μg/ml) behaved similarly to the placebo group, with only 22% of these patients experiencing grade 3 mucositis on day 15. In the low-dose groups, 0.01 μg/ml or 0.10 μg/ml GM-CSF, the incidence of day 15 grade mucositis was 56 and 66%, respectively. These results could not be explained by differences in leucocyte toxicity between the groups.

Haus and colleagues [39] treated chemotherapy-induced mucositis with mouthwash solutions containing 5–10 μg/ml GM-CSF (4–6 times daily for 10 days) in patients suffering from various neoplasms. The authors observed a decrease of duration and severity of chemotherapy-induced oral mucositis.

2 patients, 1 with Kaposi's sarcoma lesions of the oropharynx and the other with non-Hodgkins lymphoma (NHL) of the paranasal sinuses developed grade 3 mucositis after radiotherapy [40]. Treatment of mucositis consisting of a solution of 300 μg in 250 ml of water as mouthwash for 1 h/day was started at the time of occurrence. This limited experience with GM-CSF suggested that this drug might be useful to improve acute mucosal toxicity in patients undergoing irradiation of the upper aero-digestive tract mucosa.

The local use of GM-CSF in the treatment of severe mucositis was evaluated in 14 patients with different kinds of cancer by Cinat and colleagues [41]. All patients were treated with different regimens of chemotherapy containing 5-FU, folinic acid, methotrexate, doxorubicin, etoposide and/or ifosfamide. GM-CSF was employed as a 15 min mouthwash solution at a 1 mg/ml concentration. The average total recovery time was 9 days (range: 6–14 days) which compared to the expected duration of 14–28 days suggesting that the use of local GM-CSF may have shortened the natural history of mucositis.

40 patients entered the study initiated by Ibrahim and Al Mulhim [42] to evaluate the effect of granulocyte-macrophage colony-stimulating factor on chemotherapy-induced oral mucositis. Treatment started within 24 h of occurrence of mucositis and consisted of 5 μg/ml to 10 μg/ml GM-CSF as mouthwash solution, 4–6 times daily. The duration of treatment was 10 days (stopped earlier if mucositis resolved). The use of GM-CSF mouthwash was not associated with any apparent adverse effect. It was found that GM-CSF, as used in this trial, had a significant recuperative efficacy on the severity, morbidity and duration of chemotherapy-induced oral mucositis.

CONCLUSION

Ulcerative oral mucositis is a common side-effect of many forms of cancer chemotherapy and has an overall frequency of approximately 40%. Oral mucositis causes discomfort, pain and interferes with oral nutrition. Mucositis can be a potential source of infection. The treatment of this often very severe side-effect is of particular interest because it frequently limits the administration of the planned treatment.

Scant information is available regarding the prevention and treatment of chemotherapy- and radiotherapy-induced mucositis, despite a phlethora of prescribed remedies. Currently, there are no means to prevent stomatitis except to modify the doses of the offending chemotherapeutic agents. Meticulous oral hygiene will help to diminish pathogenic oral flora and decrease the risk of secondary infections. Treatment with topical oral anaesthetics, such as viscous xylocaine, can relieve pain and help to maintain adequate oral intake. GM-CSF probably can reduce the severity and duration of chemotherapy-induced oral mucositis and improve the pain and eating function after chemotherapy. Owing to the small number of patients, and the different types of chemotherapy regimens which cause distinctly different grades and length of oral mucositis, of the trials that have been performed, the role of GM-CSF as topical treatment in the reduction of chemotherapy-induced oral mucositis warrants further clinical investigations.

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