INTERNATIONAL JOURNAL OF
TOBACCO AND ORAL HEALTH

IJTOH 2015;1(1):9-13
Jan-Jun

Preventive Strategies in Management of Oral Mucositis

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Abstract

Oral mucositis is a painful, debilitating, dose-limiting side-effect of radiotherapy, chemotherapy, and radio-chemotherapy in patients with cancer. Severe oral mucositis can lead to the need to interrupt or discontinue cancer therapy and thus may have an impact on cure of the primary disease. Mucositis may also increase the risk of local and systemic infection and significantly affects quality of life and cost of care. This article reviews the current knowledge on the pathogenesis, clinical presentation, diagnosis, and management of Oral mucositis.

Key Words

Oral mucositis; diagnosis; prevention; treatment; chemotherapy; radiotherapy

INTRODUCTION

Mucositis induced by anti-neoplastic drugs is an imperative, dose-limiting adverse effect of cancer therapy. Oral mucositis (OM) refers to erythematous, erosive, and ulcerative lesions of the oral mucosa seen in: 1) head and neck cancer patients undergoing radiation therapy; 2) patients receiving high-dose chemotherapy for cancer.[1]The severity of disease depends on diagnosis, age, oral health status and type, dose, and rate of drug administration (Table 1).[2,3] A large amount head and neck cancer patients are treated with radiotherapy, often in combination with surgery or chemotherapy. OM occurs in majority of head and neck cancer patients receiving conventional fractionated radiotherapy (one dose/day, 5 days/week for 5-7 weeks) and in 100% of patients receiving altered fractionation radiotherapy (two or more doses/day).[4] It is also a significant complication of high-dose chemotherapy in cancer patients. This article reviews the current knowledge on the clinical presentation, diagnosis, and treatment of OM which is a dose-limiting toxicity of cancer therapy.

Patho-biology of Mucositis

In 1998, Sonis proposed a four-stage model for the pathogenesis of OM (Table 2).[2]

Clinical Features

OM typically begins as erythema of the oral mucosa, followed by ulceration that may be covered by a white pseudo-membrane (Fig 1). The lesions are characteristically painful resulting in compromise nutritional intake. There is history of either systemic chemotherapy or radiation therapy to fields including the oral cavity**.** Lesions typically occur 1 to 2 weeks after chemotherapy has been delivered or after more than 30 Gy of Radiotherapy have been delivered.[5] These lesions usually heal within approximately 2 to 4 weeks after the last dose of therapy has been delivered. They are usually limited to non-keratinized tissues such as lateral and ventral tongue, buccal mucosa, and soft palate.[6]

Measurement

A number of subjective and objective scales have been used to measure OM. The measurement of the severity of OM can be used to determine disease. The World Health Organization (WHO) scale is a simple five-point scale that combines subjective and objective measures of OM (Table 3).[7]

Management

The management approach of OM is given below:

Oral Care

Maintaince oral hygiene has been reported to result in reduced incidence and severity of OM.[8] Clinical practice guidelines for OM developed by the Mucositis Study Section of the Multinational

Table 1: Main chemo-therapeutic agents responsible for oral mucositis

Alkylating agents	Busulfan,Cyclophosphamide, thiotepa, procarbazine
Anthracyclines	Doxorubicin, epirubicin, daunorubicin
Anti-metabolites	5-FU, methotrexate, hydroxyurea
Antitumor agents	Actinomycin D, bleomycin, mitomycin
Taxanes	Paclitaxel
Vinca alkaloids	Vincristine, vinblastine

Table 2: The four phases of the biologic process of mucositis

Phase	CAUSE
Inflammatory/vascular	Due to the effect of chemo- radiation in causing the release of inflammatory cytokines from the epithelium and the connective tissues. This phase is relatively acute.
Epithelial	Due to cytotoxic agents that target DNA synthesis of the oral mucosal epithelium. This phase is usually the most profound in terms of production of ulcerative lesions.
Ulcerative/microbiological	Due to breakdown in mucosal barriers. Most symptomatic and biologically complex of the phases. This phase has the greatest impact on patients' well-being and risk of oral infection.
Healing	Due to renewed cell proliferation and differentiation, return to normal peripheral blood counts, and control of oral bacterial flora. The speed at which this phase takes place directly affects the duration of the mucositis condition.

Table 3: WHO scale for Oral Mucositis

Grade 0: No oral mucositis
Grade 1: Erythema and soreness
Grade 2: Ulcers, able to eat solids
Grade 3: Ulcers, requires liquid diet because of mucositis
Grade 4: Ulcers, alimentation not possible because of mucositis

Table 4: Diet in oral mucositis

Diet that is acceptable	Things to avoid	Habits to avoid
Liquids	Spices	Smoking
Purees	Salt	Alcohol
Ice	Acidic Fruit (Grape fruit, Lemon, Orange)	
Custards		
Non Acidic Fruits (Banana, Mango, Peach, Melon)		
Eggs		
Cheeses		

Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) include a suggestion that oral-care protocols that include patient education be used in an attempt to reduce severity of OM.[9] These include: oral prophylaxis before cancer therapy, if possible twice daily tooth brushing with a soft-bristled toothbrush and fluoride-containing toothpaste. The use these toothpastes help in prevention of dental caries secondary to xerostomia. Rinsing with saline or two table spoons of sodium bicarbonate (baking soda) helps to decrease viscosity of saliva. Regular flossing should be done unless contraindicated by low platelet or neutrophil count. Limiting the use of removable dentures as far as possible to minimize trauma to the oral tissues and decrease risk of infection.

Pain Control

OM causes pain in most patients. This pain adversely effects nutritional intake, oro- dental care, thus affecting quality of life. Therefore, palliation of mucositis pain is a decisive component in managing these patients. Some patients may benefit from the use of topical anesthetics such as lidocaine. Use a combination of lidocaine and a coating agent such as magnesium hydroxide and aluminum hydroxide with or without diphenhydramine. These combinations are sometimes referred to as ''**miracle mouthwash'' or ''magic mouthwash**.'' Regardless of the use of topical agents, systemic analgesics are needed to achieve satisfactory pain control in most patients with OM. Although non-opioids should be considered first, many patients need opioid analgesics such as oxycodone. The use

of opioid analgesics commonly causes nausea, somnolence, and constipation and can, rarely, cause respiratory depression and arrest.[9]

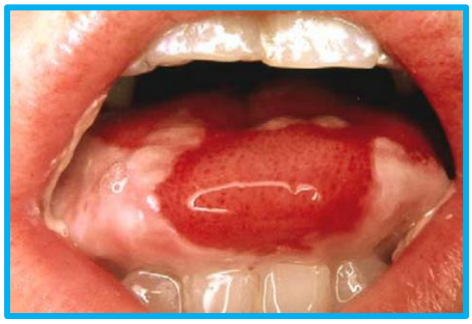

Fig. 1: Chemotherapy- induced oral mucositis

Nutritional support:

Severe OM significantly effects nutritional intake, primarily because of pain. In addition, taste changes have also been reported secondary to both chemotherapy and radiotherapy and further effects oral feeding(1). Patients should been encouraged to ingest soft, nonirritating foods or liquid diet supplements (Table4)(7). Patients should be weighed regularly to monitor weight loss. A significant proportion of patients are not able to maintain adequate nutrition by mouth and require feeding by gastric tube or intravenous line. A dietician and the patient's care takers should be involved in maintaining nutritional support.

Therapeutic Interventions

Cryotherapy: Is rapid cooling of the oral cavity using ice, it causes local vasoconstriction and hence reduces blood flow to the oral mucosa. For cytotoxic and neoplastic drugs such as 5-fluorouracil, which have a short half life and are sometimes administered as a bolus injection, it may reduce the amount of drug reaching the oral mucosa, and may therefore reduce mucositis caused by local cytotoxic activity of these drugs.[10]

Amifostine: It is a radio-protectant that has been widely used for prevention of oral mucositis induced by chemotherapy or radiation therapy. This agent is believed to act as a free radical scavenger, protecting against ROS generated by exposure to radiation. Amifostine has been approved in the United States for reducing the incidence of severe xerostomia in patients with head and neck cancer associated with radiation therapy but has not been approved for oral mucositis. For future direction, further randomized trials should be conducted on the beneficial effects of amifostine in patients receiving radiation and chemotherapy.[11,12]

Antibiotics: Many authors suggest the inclusion of prophylactic antibacterial and/or antifungal treatments to reduce the oral microflora before and during chemo/radiotherapy. Antimicrobial agents used include nystatin, clotrimazole and PTA lozenges.[13] Antibiotic lozenges designed to dissolve in the mouth and decontaminate the oral mucosa have been developed and have been widely recommended to reduce oral infections associated with mucositis. The lozenge contains polymixin E, tobramycin and amphotericin B, which together provide broad spectrum antibacterial and antifungal cover. These are commonly known as PTA lozenges or PTA pastilles. Acyclovir is an antiviral agent which is active against the Herpes species that commonly infect the oral mucous membranes in immuno-suppressed cancer patients. It appears that prophylactic administration of the drug may have some value in reducing oral lesions due to Herpes in susceptible patients, but as the majority of mucositis lesions do not result from a virus they are not affected by this agent.[13]

Laser therapy: Three controlled studies have examined the effects of low-energy Helium-Neon laser therapy on OM (two on chemotherapy-induced OM and one on RT-induced OM. All three studies found a beneficial effect of the laser therapy on severity and pain of OM. It has been suggested that low-energy laser therapy may positively effects healing of mucositis lesions.[14,15]

Palliation of dry mouth: Patients undergoing cancer therapy often develop transient or permanent Xerostomia (subjective symptom of dryness) and hyposalivation (objective reduction in salivary flow). The following measures can be taken for treatment xerostomia: Drink plenty of fluids to improve dryness of the oral cavity. Several artificial substitutes for saliva are readily available can be used. Stimulation of salivary flow can also be done by chewing sugar-free gums.[16]

Granulocyte and granulocyte macrophage colony-stimulating factors: These factors belong to a family of glycoprotein growth factors, which promote the proliferation and differentiation of neutrophil and enhance the effect or functions of mature neutrophil .Clinical experience has also shown that these could stimulate the cells of the mucous membranes of the oro-pharynx. These protein not only causes a reduction in the degree of neutropenia, but chemotherapy-induced mucositis is significantly reduced.[17]

Management of bleeding: In patients who are thrombocytopenic due to high-dose chemotherapy bleeding may occur from the ulcerations of oral

mucositis. Intraoral bleeding can usually be controlled with the use of topical haemostatic agents such as fibrin glue or gelatin sponge. Patients whose platelet counts fall drastically require platelet transfusion due to risk for spontaneous internal bleeding.[18]

CONCLUSION

OM is a significant and dose-limiting toxicity of cancer therapy, with important clinical and financial implications. OM is diagnosed clinically based on history of therapy, clinical appearance, symptoms, onset, duration, and location of lesions. The primary management considerations are maintenance of good oral hygiene, pain control, and nutritional support. Clinical practice guidelines for the management of OM are now available. The dental professional should work closely with the medical providers in the management of OM.

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