Prevention and Management of Mucositis in Patients with Cancer: a Review Article

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Abstract

After chemo/radiation therapy, mucositis is one of the most common side effects, so timely nursing care and instructed home care, significantly could decrease cost of medical care, and then increase quality of life.

This review summarizes preventive and therapeutic intervention of mucositis (localized or systemic), between some of patients with cancer.

Keywords: Mucositis; Radiotherapy; Primary prevention; Therapeutics

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Introduction

Oral complications after high doses of chemotherapy and radiation therapy during the Hematopoietic Stem Cell Transplantation (HSCT) cause high morbidity and could affect transplant outcome [1]. Oral Mucositis (OM) leave one of the worst impressions on medical and economic success of HSCT [2]. The rupture of oral cavity's epithelial defence due to the cytotoxic effect of the myeloablative regimen, together with the sub-mucosal involvement, lead to several clinical events, such as opportunistic infections, pain, and difficulties in mastication and swallowing [3, 4]. This might result in severe nutritional deficiencies, then cause to parenteral nutrition and more hospitalization. All these factors significantly affect the patient's quality of life and patient costs. "OM" has seen most often in: very young-very old and female patients with cancer. Then "myeloablative regimen" and "type of transplant" have been the other important risk factors for "OM" [5]. Mucositis evolvement recognizes not only through direct cell injury mediated by chemotherapy or radiation, but also more significantly as a consequence of a complex cascade of biological events [6]. Regarding to the type of transplant, there are evidences that patients which have submitted to allogeneic transplant develop OM more frequently and more severely than autologous transplant patients. About 75% of allogeneic transplanted patients will show severe OM. This could be due to the cytotoxic drugs that have used for prevention of Graft Versus Host Disease (GVHD), which are highly toxic to the mucosal cells. These medicines have reduced the regenerative capacity of the oral mucosa thereby prolonging the mucositis and increasing its severity [7]. There is no consensus about the most efficient protocol to prevent and treat OM. Several treatments have been testing, including the use of a keratinocyte growth factor, benzydamine; mouth rinses with antimicrobial agents such as chlorhexidine; and cryo or laser therapy during chemotherapy [8, 9]. Regardless of selected treatment, meticulous oral hygiene is essential for OM control [10].

Considering mucositis as a systemic process, rather than limited one, provides supports for use of systemic treatments instead of merely oral rinses [5].

Application of laser therapy reduces the extension and severity of oral mucositis in patients after hematopoietic transplant [1].

Analgesics like morphine have recommended for oral mucositis in hematopoietic stem cell transplant patients. Sucralfate and antimicrobial lozenges have not recommended for prevention of radiation-induced oral mucositis. Benzydamine has recommended for radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose therapy. Cryotherapy has recommended for bolus 5-Fluorouracil (5-FU) then has suggested for bolus edatrexate and high-doses of melphalan. Keratinocyte growthfactor-1 (palifermin) has recommended 3 days before conditioning treatment then 3 days post-transplant for patients whose have received high-dose chemotherapy and total body irradiation with autologous stem cell transplant in hematologic malignancies. Granulocyte-macrophage colony stimulating factor mouthwashes have not recommended for prevention of mucositis.

Recommendations for oral care include:

_ Collaborate with a multidisciplinary team in all phases of treatment.

_ Brush all tooth surfaces for at least 90 seconds, at least twice daily by a soft toothbrush.

_ Allow toothbrushes to air dry before storing.

_ Floss at least once daily or as advised by clinician.

_ Rinse mouth four times daily with a bland rinse.

_ Avoid tobacco, alcohol, irritating foods (acidic, hot, rough, and spicy).

_ Use water-based moisturizers to protect lips.

_ Maintain adequate hydration.

_ Provide written instruction and training for patients about the above items. Verify understanding with return explanation and demonstration.

_ Bland rinses (normal saline, sodium bicarbonate, and a saline and sodium bicarbonate mixture) to remove loose debris and aid with oral hydration have also recommended in stem cell transplantation [3, 11].

If feasible, establish formal protocols and guidelines that are adaptable, appropriate and efficient for:

- Adults
- Children
- Elderly
- Patients with cognitive or sensory impairment

Before cancer therapy, optimize oral health:

- Consider evaluation by dental professional
- Eliminate/reduce oral infections, periodontal disease, gingivitis, deep caries/ pulp infections
- Remove/modify potential sources of trauma/irritation Sharp teeth/fractured restorations
- Poorly fitting or broken removable dentures
- Orthodontic brackets or wires
- Reduce risk for secondary infection [12]

As there is no universally accepted medical or hygienic solution for prevention of mucositis, treatment of the problems experienced by patients with mucositis is an area for nursing intervention. Three important areas of focus include: treatment of pain, dryness, and ulcerations [13].

Treatment of Pain

Although topical coating agents might be initially effective for pain relief of limited superficial lesions and morphine mouthwash has examined as a topical treatment, considering mucositis as a systemic process provides theoretical support for the use of systemic modes of pain relief associated with severe mucositis [14-19] (Table 1).

Treatment of Dryness

Non-irritating rinses, sucking ice, and sips water might be perceived as beneficial. Mouth moisturizers may also promote comfort [20].

Treatment of Ulcerations

Frequent rinsing with a non-irritating solution is extremely important and might decrease risk of septicemia. However; patient's compliance would strongly depended on the quality of the pain control [3]. The most effective self-care behaviours for Radiation Therapy (RT)-induced mucositis pain were mouth rinsing and oral analgesics usage [21].

Animal trials data and preliminary data in patients indicate that cytokines such as interleukin-1, interleukin-11, Transforming Growth Factor beta 3 (TGF-b3) and keratinocyte growth factor could reduce the incidence of mucositis. Other potentially useful agents are the angiogenesis-inhibiting medicines; thalidomide, the cytoprotector; amifostine and the pineal hormone; melatonin [22].

It is estimated that oral mucositis is a complication in 40% of patients receiving chemotherapy, 75% of those exposed to high doses of chemotherapy and more than 90% of those irradiated for head and neck cancer [23, 24]. Ulcerative mucositis not only is extremely painful, but also constitutes a risk for systemic infections, especially in neutropenic patients. The pathophysiology of mucositis has not known in detail. Irradiation and chemotherapeutic agents such as 5-fluorouracil and methotrexate, could induce a direct toxic effect on the oral mucosa, but in patients receiving other types of chemotherapy, mucositis is most often have pronounced during the period of febrile neutropenia [25]. Furthermore mucositis is due to oral infections in a number of patients [26]. Recently, a new hypothesis for development of chemotherapy-induced stomato toxicity has proposed. According to this, mucositis is a complex process, which has divided into four phases, called the inflammatory phase, the epithelial phase, the ulcerative: bacteriological phase and the healing phase. This hypothesis also has denoted on the importance of various cytokines in the development and treatment of mucositis (Table 2). A number of locally applied agents have been investigated to prevent or treat mucositis. These include sucralfate, vitamin E, chlorhexidine, anti-inflammatory agents, cytokines, Prostaglandin E1 (PGE-1) and PGE-2, multi agents topical mouth rinses, leucovorin and allopurinol. Systemically applied treatments for mucositis, investigated in trials include antioxidants (b-carotene, azelastine), immune modulatory drugs such as indomethacin and pentoxifylline,

Table 1. Patient-related factors cause to worse mucositis

Age	Very young: increased turn over Very old: decreased healing
Gender	A mild trend to female
Oral hygiene	Poor Oral hygiene
Salivary secretory function	Decreased flow rate or quality of saliva
Smoking	Change microbial flora Delayed healing
Body mass index	Poor nourished people
Genetic	Some patients are resistant to mucositis
Renal capacity	Elevated creatinine leads to mucotoxicity
Previous chemotherapy	Weakness of mucosa because of previous mucositis

Table 2. Recommendations for mucositis management

Solutions for mucositis problem			Prevention for mucositis
Pain relief	Treatment of dryness	Treatment of ulceration	
Topical coating agent Morphine mouthwash	Non irritating rinses Sucking ice Sipping water	Non irritating solutions	Oral pilocarpine GMCSF not recommended

anticholinergic drugs, cytokines, antiviral drugs and glutamine. The anti-cholinergic medicine propantheline has been able to decrease etoposide-induced mucositis, compared with placebo or historical controls, in small studies [27]. Acyclovir is effective in prevention of reactivation of HSV and reduces incidence of oral ulcerations, but does not influence overall oral toxicity or the need for antibiotics [19]. Cryotherapy has caused local vasoconstriction and thereby reduces blood flow of the oral mucosa. Drugs currently under investigation include keratinocyte growth factor, interleukin-1 and 11and TGF-b. Both the cytoprotector, amifostine and the pineal hormone; melatonin have been claimed to have some effects in the prevention of mucositis. It has denoted that the potential mechanism of "c thalidomide" action might include inhibition of cytokines such as interleukin-1, interleukin-6 and TNF-a, that are supposed to take part in the pathogenesis of oral mucositis [28].

The literature indicates that honey could promote wound healing, so the authors have investigated whether its anti-inflammatory properties might limit the severity of radiation-induced oral mucositis. Honey is strongly protective (RR= 0.067) against the development of mucositis. The proportion of patients with intolerable oral mucositis was lower in the honey group and this was statistically significant (p=0.000). Honey is readily available, affordable and well accepted by patients, making it useful for improving the quality of life in irradiated patients [29].

Oral Pilocarpine (OP) is highly effective in the prevention of oral mucositis when given prophylactically to adult patients receiving a variety of cancer chemotherapy regimens. It should notice that pilocarpine is a parasympathomimetic medicine should be prescribed cautiously, because of side effects such as stomach ache, nausea, tachycardia and extreme sweating. Reasons for this positive effect are not clear. OP is known to increase salivary flow by stimulating the salivary glands, especially the minor salivary glands. Minor salivary glands are responsible for production of 70% of the total salivary mucin. OP stimulates the production of salivary mucin, proteins and glycoproteins. It seems that mucin and other salivary constituents play a protective role in prevention of chemotherapy-induced mucositis [30, 31].

Nowadays a novel preventive agent for mucositis is a milk-derived protein extract (pv701) in form of mouthwash. This agent is used in patients with lymphoma who were given carmustine, etoposide, cytarabine, and melphalan (BEAM) chemotherapy. Simultaneously initiating with BEAM regimen, this agent has administered as 1215 mg/day, 6 times daily for 12 days then continue for one week after chemotherapy. It should note in patients who have received autologous stem cell after BEAM has been

completed. In comparison, patient who has received pv701 experienced significantly less frequent higher grades of mucositis. Duration of admission to intensive care unit and enteral/parenteral feeding was significantly reduced [32, 33].

On the other hand some of the previously preventive prescribed medicines currently have demonstrated not only no significant benefit but also serious complications [34-37]. Makkonen has reported no advantages from subcutaneously administration of 150-300 microgram Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) after 10 Gy radiotherapy. His study has shown 65% skin reaction in injection site, 30% fever, 25% bone pain and 15% nausea [38].

Its worthy of mention, regarding that mucositis is unavoidable in patients after chemo/radiation therapy, it is advisable to improve quality of life and decrease the severity of complications with timely nursing care and palliative medicines.

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Conflict of Interest

There is no conflict of interest in this article.

Authors' Contribution

Fatemeh owlia designed the study, reviewed the literatures and wrote the paper. Seid Kazem Kazemeini contributed to literature review and Neda Gholami contributed to writing the manuscript. All authors read and approved the final manuscript.

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