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Review Article

Treatment and Prevention of Oral Mucositis: A Literature Review

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Abstract

Oral health is a cardinal element of nutritional as well as systemic well-being and plays a substantial part in sustaining optimum general health condition. Various factors influence oral health including metabolic diseases such as endocrine, hematological, gastrointestinal, cutaneous, and neurological diseases. The intent of this review is to highlight the treatment as well as prevention strategies for one of the most devastating repercussions of chemotherapy (CT) and radiotherapy (RT) on the oral cavity in the form of oral mucositis (OM). A review of literature was performed using relevant key words ("Mucositis" OR "Oral Mucositis" OR "Oral Stomatitis" AND "Treatment of Mucositis" OR "Treatment of Oral Mucositis" OR "Treatment of Oral Stomatitis" AND "Prevention of Mucositis" OR "Prevention of Oral Mucositis" OR "Prevention of Oral Stomatitis") in prominent journals pertaining to Oncology and Dentistry (*CA: A Cancer Journal for Clinicians*, *Cancer, Frontiers in Oncology*, *Journal of Clinical Oncology*, *and Oral Oncology*). It is basically sequelae of CT, RT, and radiochemotherapy in patients suffering from malignant diseases as well as those who require hematopoietic stem cell transplants. In addition to its negative effects on the oral cavity and consequently on the overall quality of life, OM may lead to delay in cancer treatment which incriminates in a poor prognosis of the disease.

Keywords: Oral mucositis, prevention, treatment

Introduction

Mucositis (sometimes referred to as stomatitis) is a condition of inflammation and deterioration of the mucous membrane lining of the gastrointestinal tract and oral cavity.[1] It is almost an inevitable after the effect of high-dose radiation therapy. The major determining factor, whether oral mucosa or gastric mucosa will be affected, is the cancer treatment regimen that is being employed. Apart from being caused by chemotherapy (CT) and radiotherapy (RT), mucositis can also occur in people receiving bone marrow transplants (BMTs).[2]

Literature Search Methodology

An electronic search was performed, from January 1990 to December 2018, to identify articles on the treatment and prevention protocols for CT- and RT-induced oral mucositis (OM). Related articles published in the English language and prominent oncology as well as dentistry journals were included.

- *CA: A Cancer Journal for Clinicians*
- *Cancer*
- *Frontiers in Oncology*
- *Journal of Clinical Oncology*
- *Oral Oncology*.

The keywords used for the search strategy are as follow:

- "Mucositis" OR "Oral Mucositis" OR "Oral Stomatitis"
- "Treatment of Mucositis" OR "Treatment of Oral Mucositis" OR "Treatment of Oral Stomatitis"
- "Prevention of Mucositis" OR "Prevention of Oral Mucositis" OR "Prevention of Oral Stomatitis."

Treatment of Oral Mucositis

Any single agent has not been recommended by the United States food and drug administration (US-FDA) to treat OM. Reduction of symptoms and prevention of complications, including pain control, combating secondary infections, nutritional support, and prophylaxis are regarded as

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Table 1: Prevention and management options of oral mucositis

Prevention	Management
Oral hygiene maintenance	Locally applied agents (glycyrrhetinic acid/sodium hyaluronate gel)
Cryotherapy	L-glutamic acid
Keratinocyte growth factor	Manganese superoxide dismutase
Amifostine	Local anesthetics
Helium-neon laser	Oral and systemic anesthetics
IMRT	Antibacterials, antifungals, and antivirals
Miscellaneous protocols	Cellular therapies

IMRT – Intensity-modulated radiation therapy

the cornerstone in the management of OM [Table 1].[3] According to recently updated evidence-based clinical and preclinical investigations, these agents are discussed as follow.[4]

Locally applied agents

Glycyrrhetinic acid/sodium hyaluronate gel has a mechanical effect in pain management associated with OM. It soothes oral lesions by adhering to the mucosal surface of the oral cavity. Nevertheless, there are controversies related to the preclinical studies, and only one clinical testing without any known result was carried out until now.[4]

L-Glutamic acid

It is a nonessential amino acid that neutralizes RT-induced metabolic deficiencies.[5] Locally administered L-glutamine alleviated RT-induced OM in randomized clinical experiments.[6] Oral suspension of glutamine powder was approved for topical use by the US-FDA for management of CT-induced OM.[7]

Manganese superoxide dismutase

It acts as a detoxifying agent and removes reactive oxygen species (ROS). It was believed of having radioprotective effects against RT-induced colitis, eye and intestinal injury, hepatic cells apoptosis, and esophagitis.[8] Phase 1 dose escalation research of GC4419 in conjunction with RT/CT for squamous cell carcinoma of head and neck has recently been finished awaiting release of results (NCT01921426).

Local anesthetics

For the purpose of short-term pain relief associated with OM, local anesthetics such as lidocaine, diphenhydramine, xylocaine, and dyclonine hydrochloride are used, despite the fact that they may meddle with sensation of taste leading to hypoalimentation.[9]

The magic mouthwash, benzocaine-containing lozenges, and morphine mouthwashes are preferably being used for lessening oral pain associated with OM.[10]

Promising results are shown by the application of corticosteroid mouthwashes, but there is a gap related to its large-scale data availability that should be connected by relevant clinical trials.[11]

In mild cases of Radiation-induced oral mucositis (RIOM), artificial saliva spray is frequently used to reduce mucosal dryness.[12]

Chamomile has antiseptic, antibacterial, anti-inflammatory, and anti-spasmodic effects. In CT-induced mucositis, it has investigated as an emulsion therapy with encouraging result.[13] However, studies are required for its use in RIOM for determining its efficacy.[4]

Honey has a mucoprotective effect. It has been investigated in several preclinical trials that is reduces the severity and incidence of RIOM.[14,15] However, when Manuka honey was used, the available clinical trial contradicted the preclinical studies' results.[16] More research is needed to ensure honey's therapeutic potential in RIOM.[4]

Vitamin A (retinol) and its derivatives have epithelial proliferative and anti-inflammatory effect.[17] During BMT, topical tretinoin has shown to alleviate oral complications.[18]

Tocopherol (Vitamin E) reduces the oxidative injury of the oral mucosa and lessens the risk of symptomatic RT-induced OM in head-and-neck carcinoma patients in randomized, double-blind clinical experiments.[19]

A randomized clinical trial showed that sodium alginate mitigates severity and pain of RIOM.[20]

Povidone-iodine, an antifungal, antiviral, and antibacterial agent, curtails the duration, incidence, and severity of concurrent chemoradiotherapy (CCRT)-induced OM. Furthermore, it is economical and easily applied.[21]

Capsaicin, a neutrophilic inhibitor, diminishes pain sensation. One clinical study showed that oral capsaicin temporarily relieved pain associated with mucositis caused by RT and CT.[22] However, further research is required to enhance its analgesic effect.[4]

Oral and systemic analgesics

Cyclooxygenase-2 (COX-2) inhibitors, having a different mechanism of action, were practiced in the management of RIOM. They suppress nuclear factor-κappaB (NF-κB), inhibit angiogenesis, and tapper off cytokine generation.[23] A randomized placebo-controlled experiment demonstrated that indomethacin, a COX-2 inhibitor, significantly abated the severity and deferred the onset of RIOM.[4]

Moreover, prostaglandin E1 and E2 demonstrated improvement in CT/RT-induced OM in some studies, but there are still controversies associated with their application.[24]

N-acetylcysteine, an antioxidant that suppresses activation of NF-κB,[25] has a radioprotective function in RT-induced liver toxicity, dermatitis, intestinal injury, and bone injury,[26] and hence, it was recommended as a nominee for a trial in RIOM. In a placebo-controlled Phase 2 experiment done on patients suffering from head-and-neck carcinoma, N-acetylcysteine significantly mitigated the severity of RIOM.[27]

Granulocyte-macrophage colony-stimulating factor (GM-CSF) and CSF recruit neutrophils to the site of tissue injury when administered systemically.[28] In several studies, when GM-CSF mouthwash is applied locally, it remarkably relieved RIOM.[29] However, some other studies did not demonstrate the same result.[4] Controversies surround the therapeutic potential of GM-CSF when applied systemically and necessitates further research.[4]

Transforming growth factor-β3, inhibitor of oral basal cell proliferation, mitigates the risk of CT-induced OM.[30] However, a valid clinical trial is necessarily required to evaluate its therapeutic potential in RT.[4]

In a randomized clinical experiment, antioxidative effect of beta-carotene[31] was implemented and it showed a significant alleviation in the risk of OM in CCRT.[32]

Analgesics are a substantial contender for pain relief associated with RIOM.[33]

Azelastine, a potent histamine antagonist, anti-inflammatory, and antioxidant have been demonstrated as a reliable agent in lessening the severity and risk of OM with CCRT.[4]

Immunoglobulins, which act as immune modulators and anti-inflammatory agents, are administered intramuscularly or intravenously as a therapeutic and prophylactic option for RT-induced OM.[4]

Agents for alleviating oral microbial burden

Antimicrobial agents

A fast track designation has been granted for brilacidin-OM (an oral rinse) by FDA. To assess its efficacy and safety, there is a Phase 2 clinical trial being carried out (NCT02324335).

Antifungal agents

Although they do not contribute directly in development of RIOM, yet they can complicate the condition, especially in patients who are immunocompromised. Fluconazole, clotrimazole, and amphotericin B play a handful role in reducing the severity of RIOM.[4,29,34] However, carrier allergy of amphotericin B limits its application.[35]

Antibacterial agents

The main culprits in the generation of secondary infection stage in RIOM are aerobic species (e.g., *Staphylococcus epidermidis* and *Pseudomonas* spp.), endotoxins of aerobic Gram-negative bacilli, and anaerobic bacteria (e.g., Veillonella spp., and *Bacteroides* spp.).[29] Mouthwashes containing ciprofloxacin, ampicillin, and tobramycin have demonstrated symptoms relieving effects in RIOM.[4,36-38]

Antiviral agents

Herpes simplex virus type-1 and varicella-zoster virus are most frequently seen viral infections in individuals who are myelosuppressed and seropositive.[39] A marked diminishing of the oral herpetic infections was noted when acyclovir was administered topically and systemically. However, no prophylactic role was evident against OM itself.[40]

Cellular therapies

Bone marrow-derived mesenchymal stromal cells (BM-MSCs) therapy has been employed in fractioned RT-induced OM, where the application systemic single dose of 6 million mesenchymal stromal cells (MSCs) resulted in a compelling reduction in ED50 (the RT dose that formed ulcer in half of the irradiated mice).[41] The first ever MSCs therapy was performed in 2014.[41] They reckoned that transplantation of bone marrow or BM-MSCs s could regulate RIOM in fractioned RT, depending on transplantation time.[41] Nonetheless, in another research, the researchers came to a conclusion that there are no therapeutic advantages of BM-MSCs on RIOM in single-dose RT as compared to the therapeutic impact of the operation of endogenous bone marrow stem cells.[42] On the bedrock of initial studies, more research is required in this area.[4]

Prevention of Oral Mucositis

Along with curtailing the progression of OM, its risk can also be prevented by maintaining good oral hygiene. We will review contemporary measures and agents for preventing OM[4,43] [Table 1].

Good oral hygiene

It has been proved as one of the most efficient methods to lessen the risk of OM and attenuate its advancement. Pre-existing oral pathology, for instance, xerostomia, dental caries, pulpal disease, and periodontal lesions are associated with escalated bacterial colonization and severe OM. Before initiating any mucotoxic therapy for cancer, it is recommended to have an early oral inspection. To alleviate the adverse effects of anticancer therapy on the oral cavity, it is proposed to eradicate any preexisting oral pathology before commencing RT. This may be attained by executing early serological, histological, microbiological, and cytological examinations.[29]

The International Society of Oral Oncology (ISOO) and Multinational Association of Supportive Care in Cancer (MASCC) guidelines suggest the application of standardized oral care protocol, for example, flossing, use of toothbrush having soft bristles, and utilization of nonmedicated rinses ($NaHCO_3$ and saline).[3,4] It is summarized as follows:

- Daily brush with an ultrasoft toothbrush with fluoride toothpaste
- Scaling
- Rinse by using nonirritating solution, that is, saline to enhance the quality of saliva
- Soft diet having low sugar content
- Non-acidic drinks and food
- Flossing is not advised as platelet count is low
- Minimum use of denture
- No smoking or alcohol
- Other preventive methods such as reducing the microbial load and patient education on good oral hygiene.

A summary of diet and habits that are acceptable as well as nonadmissible during OM is given in Table 2.

Table 2: Recommended diet in patients with oral mucositis

Admissible diet	Nonadmissible diet	Nonadmissible habits
Eggs	Salty food	Tobacco smoking
Cheese	Acidic fruits (lemon, orange, etc.)	Alcohol consumption
Fresh juices	Spicy food	Betel quid chewing
Ice	Junk food	Cheek biting
Nonacidic fruits (mango, banana, etc.)		

Cryotherapy

Cryotherapy has been proposed for CT-induced OM, but no establish role in RIOM inadequate evidence.[4] Recent studies have proven the use of cryotherapy for preventing OM in patients who received 5-fluorouracil. Cryotherapy is also suggested in individuals who will experience high doses of melphalan for BMT.[44]

Keratinocyte growth factor

An epithelial mitogen, that is, keratinocyte growth factor (KGF) plays a vital role in the reduction of ROS by activation of Nuclear factor (erythroid-derived 2)-like 2 and had been utilized in radiation-induced OM with promising results.[45] It seems to be one of the most auspicious preventions and treatment options for radiation-induced OM that has been examined in clinical trials.[4] Palifermin (IV recombinant human KGF-1) had been recommended by US-Food and Drug Authority (FDA) for reducing the risk of OM in patients with hematological malignancies who are receiving myelotoxic therapies and need hematopoietic cell support post reliable results in lessening WHO Grade 3 and 4 OM in such patients. Palifermin is delivered intravenously 3 days before RT/CT and for 3 days after CT. Palifermin should not be administered on the same day of CT/RT.[27]

Amifostine

Amifostine has three distinct properties, i.e., cytoprotective agent, free-radical scavenger, and antioxidant. It is conventionally administered intravenously before RT or CT. It is recommended by the US-FDA to alleviate the cumulative renal toxicity related with frequent administration of cisplatin with individuals having advanced ovarian carcinoma. Moreover, it is also approved in alleviating the risk of mild-to-severe xerostomia in individuals who are undergoing postoperative RT for head and neck cancer.[46] For mild-to-severe RT-induced xerostomia, its approved dose is 200 mg/m^2 QD over 3 min intravenously, initiating 15–30 min before standard fraction RT (1.8–2.0 Gy). Monitoring of blood pressure is imperative before, during, and after intravenous infusion. Oral administration of 5-HT3 receptor antagonists is suggested before amifostine therapy.[47]

Helium–neon laser

Low-energy helium–neon laser exercised before RT showed a substantial decline in duration and intensity of radiation-induced RT in head and neck cancer patients. The MASCC/ISOO guidelines propose the utilization of low-level laser technique in CT-induced OM at institutions that can administer the essential technology as well as training.[4]

Miscellaneous protocols

Intraoral appliances (radiation shields), 3D and RT field design, removal of prosthetics, midline mucosa-sparing blocks, and intensity-modulated radiation therapy are proven in preclinical research to lessen the radiation scatter and radiation-induced OM injury.[27]

Future prospects

Given the magnitude of the problem, oral repercussions of RT/CT are a grave concern for the public health all over the world. Their effect on individuals as well as communities due to suffering and pain, alleviated quality of life, and inability to function properly they inflict, is substantial. An extensive and exhaustive research is being done on this very topic of concern worldwide as some influential breakthroughs have been made, but there is a dire need to transform these researches into practical and clinical application.

In the contemporary era of innovation, much emphasis is being laid on the formulation of novel and offbeat techniques. Recently, there has been the development of anti-interleukin (IL)-6 antibodies and fragments having binding precision of IL-6 for prevention and treatment of OM. Likewise, tumor necrosis factor (TNF)-specific antibody is also being assessed for early interception and treatment of OM. It is believed that the inflammatory response will be shut down by the anti-TNF antibody. However, there is a set of clinical trials waiting for these novel agents.

Conclusion

The oral cavity is one of the major sites of the human body, where RT and CT can wreak havoc. OM is almost an inevitable negative repercussion of CT, RT, and radiochemotherapy. Oral complications of RT/CT, that is, mucositis is almost imminent, but their incidence and severity can be lessened by regularly visiting physician and dentist. The role of a dentist should never be underestimated or ignored in such instances as he/she plays a crucial role in preventing as well as management of oral disorders associated with RT/CT. Proper prophylaxis and management may prevent the intensity of OM and eventually leads to a better disease control.

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Conflicts of interest

There are no conflicts of interest.

References

1. Gupta A, West HJ. Mucositis (or stomatitis). JAMA Oncol 2016;2:1379.
2. Peterson DE, Lalla RV. Oral mucositis: The new paradigms. Curr Opin

Oncol 2010;22:318-22.
3. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, *et al.* MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120:1453-61.
4. Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. Front Oncol 2017;7:89.
5. Klimberg VS, Souba WW, Dolson DJ, Salloum RM, Hautamaki RD, Plumley DA, *et al.* Prophylactic glutamine protects the intestinal mucosa from radiation injury. Cancer 1990;66:62-8.
6. Huang EY, Leung SW, Wang CJ, Chen HC, Sun LM, Fang FM, *et al.* Oral glutamine to alleviate radiation-induced oral mucositis: A pilot randomized trial. Int J Radiat Oncol Biol Phys 2000;46:535-9.
7. Peterson DE, Jones JB, Petit RG 2nd. Randomized, placebo-controlled trial of saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. Cancer 2007;109:322-31.
8. Grumetto L, Del Prete A, Ortosecco G, Barbato F, Del Prete S, Borrelli A, *et al.* Study on the protective effect of a new manganese superoxide dismutase on the microvilli of rabbit eyes exposed to UV radiation. Biomed Res Int 2015;2015:973197.
9. LeVeque FG, Parzuchowski JB, Farinacci GC, Redding SW, Rodu B, Johnson JT, *et al.* Clinical evaluation of MGI 209, an anesthetic, film-forming agent for relief from painful oral ulcers associated with chemotherapy. J Clin Oncol 1992;10:1963-8.
10. Sarvizadeh M, Hemati S, Meidani M, Ashouri M, Roayaei M, Shahsanai A. Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer. Adv Biomed Res 2015;4:44.
11. Rothwell BR, Spektor WS. Palliation of radiation-related mucositis. Spec Care Dentist 1990;10:21-5.
12. Davies AN, Singer J. A comparison of artificial saliva and pilocarpine in radiation-induced xerostomia. J Laryngol Otol 1994;108:663-5.
13. Dos Reis PE, Ciol MA, de Melo NS, Figueiredo PT, Leite AF, Manzi Nde M, *et al.* Chamomile infusion cryotherapy to prevent oral mucositis induced by chemotherapy: A pilot study. Support Care Cancer 2016;24:4393-8.
14. Bardy J, Molassiotis A, Ryder WD, Mais K, Sykes A, Yap B, *et al.* A double-blind, placebo-controlled, randomised trial of active manuka honey and standard oral care for radiation-induced oral mucositis. Br J Oral Maxillofac Surg 2012;50:221-6.
15. Van den Wyngaert T. Topical honey application to reduce radiation-induced oral mucositis: A therapy too sweet to ignore? J Evid Based Dent Pract 2012;12:203-5.
16. Hawley P, Hovan A, McGahan CE, Saunders D. A randomized placebo-controlled trial of manuka honey for radiation-induced oral mucositis. Support Care Cancer 2014;22:751-61.
17. High KP, Legault C, Sinclair JA, Cruz J, Hill K, Hurd DD. Low plasma concentrations of retinol and alpha-tocopherol in hematopoietic stem cell transplant recipients: The effect of mucositis and the risk of infection. Am J Clin Nutr 2002;76:1358-66.
18. Cohen G, Elad S, Or R, Galili D, Garfunkel AA. The use of tretinoin as oral mucositis prophylaxis in bone marrow transplantation patients: A preliminary study. Oral Dis 1997;3:243-6.
19. Ferreira PR, Fleck JF, Diehl A, Barletta D, Braga-Filho A, Barletta A, *et al.* Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: A double-blind randomized trial. Head Neck 2004;26:313-21.
20. Oshitani T, Okada K, Kushima T, Suematsu T, Obayashi K, Hirata Y, *et al.* Clinical evaluation of sodium alginate on oral mucositis associated with radiotherapy. Nihon Gan Chiryo Gakkai Shi 1990;25:1129-37.
21. Roopashri G, Jayanthi K, Guruprasad R. Efficacy of benzydamine hydrochloride, chlorhexidine, and povidone iodine in the treatment of oral mucositis among patients undergoing radiotherapy in head and neck malignancies: A drug trail. Contemp Clin Dent 2011;2:8-12.
22. Berger A, Henderson M, Nadoolman W, Duffy V, Cooper D, Saberski L, *et al.* Oral capsaicin provides temporary relief for oral mucositis pain secondary to chemotherapy/radiation therapy. J Pain Symptom Manage 1995;10:243-8.
23. Lalla RV, Pilbeam CC, Walsh SJ, Sonis ST, Keefe DM, Peterson DE. Role of the cyclooxygenase pathway in chemotherapy-induced oral mucositis: A pilot study. Support Care Cancer 2010;18:95-103.
24. Kono T, Kaneko A, Matsumoto C, Miyagi C, Ohbuchi K, Mizuhara Y, *et al.* Multitargeted effects of hangeshashinto for treatment of chemotherapy-induced oral mucositis on inducible prostaglandin E2 production in human oral keratinocytes. Integr Cancer Ther 2014;13:435-45.
25. He D, Behar S, Roberts JE, Lim HW. The effect of L-cysteine and N-acetylcysteine on porphyrin/heme biosynthetic pathway in cells treated with 5-aminolevulinic acid and exposed to radiation. Photodermatol Photoimmunol Photomed 1996;12:194-9.
26. Kennedy AR. Chemopreventive agents: Protease inhibitors. Pharmacol Ther 1998;78:167-209.
27. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. Dent Clin North Am 2008;52:61-77, viii.
28. Lieschke GJ, Ramenghi U, O'Connor MP, Sheridan W, Szer J, Morstyn G. Studies of oral neutrophil levels in patients receiving G-CSF after autologous marrow transplantation. Br J Haematol 1992;82:589-95.
29. Köstler WJ, Hejna M, Wenzel C, and Zielinski CC. Oral mucositis complicating chemotherapy and/or radiotherapy: Options for prevention and treatment. CA Cancer J Clin 2001;51:290-315.
30. Sonis ST, Lindquist L, Van Vugt A, Stewart AA, Stam K, Qu GY, *et al.* Prevention of chemotherapy-induced ulcerative mucositis by transforming growth factor beta 3. Cancer Res 1994;54:1135-8.
31. El-Habit OH, Saada HN, Azab KS, Abdel-Rahman M, El-Malah DF. The modifying effect of beta-carotene on gamma radiation-induced elevation of oxidative reactions and genotoxicity in male rats. Mutat Res 2000;466:179-86.
32. Smith MA, Parkinson DR, Cheson BD, Friedman MA. Retinoids in cancer therapy. J Clin Oncol 1992;10:839-64.
33. Alfieri S, Ripamonti CI, Marceglia S, Orlandi E, Iacovelli NA, Granata R, *et al.* Temporal course and predictive factors of analgesic opioid requirement for chemoradiation-induced oral mucositis in oropharyngeal cancer. Head Neck 2016;38 Suppl 1:E1521-7.
34. Nicolatou-Galitis O, Velegraki A, Sotiropoulou-Lontou A, Dardoufas K, Kouloulias V, Kyprianou K, *et al.* Effect of fluconazole antifungal prophylaxis on oral mucositis in head and neck cancer patients receiving radiotherapy. Support Care Cancer 2006;14:44-51.
35. Lefebvre JL, Domenge C; Study Group of Mucositis. A comparative study of the efficacy and safety of fluconazole oral suspension and amphotericin B oral suspension in cancer patients with mucositis. Oral Oncol 2002;38:337-42.
36. Spijkervet FK, Van Saene HK, Van Saene JJ, Panders AK, Vermey A, Mehta DM, *et al.* Effect of selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. J Surg Oncol 1991;46:167-73.
37. Matthews RH, Ercal N. Prevention of mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol 1996;1:135-8.
38. Spijkervet FK, van Saene HK, van Saene JJ, Panders AK, Vermey A, Mehta DM, *et al.* Mucositis prevention by selective elimination of oral flora in irradiated head and neck cancer patients. J Oral Pathol Med 1990;19:486-9.
39. Prelack MS, Patterson KR, Berger JR. Varicella zoster virus rhombencephalomyelitis following radiation therapy for oropharyngeal carcinoma. J Clin Neurosci 2016;25:164-6.
40. Evans TG, Bernstein DI, Raborn GW, Harmenberg J, Kowalski J, Spruance SL, *et al.* Double-blind, randomized, placebo-controlled study of topical 5% acyclovir-1% hydrocortisone cream (ME-609) for treatment of UV radiation-induced herpes labialis. Antimicrob Agents Chemother 2002;46:1870-4.
41. Schmidt M, Haagen J, Noack R, Siegemund A, Gabriel P, Dörr W. Effects of bone marrow or mesenchymal stem cell transplantation on oral mucositis (mouse) induced by fractionated irradiation. Strahlenther Onkol 2014;190:399-404.
42. Schmidt M, Piro-Hussong A, Siegemund A, Gabriel P, Dörr W. Modification of radiation-induced oral mucositis (mouse) by adult stem cell therapy: Single-dose irradiation. Radiat Environ Biophys 2014;53:629-34.

43. Al-Ansari S, Zecha JA, Barasch A, de Lange J, Rozema FR, Raber-Durlacher JE. Oral mucositis induced by anticancer therapies. Curr Oral Health Rep 2015;2:202-11.
44. Lopes LD, Rodrigues AB, Brasil DR, Moreira MM, Amaral JG, Oliveira PP. Prevention and treatment of mucositis at an oncology outpatient clinic: A collective construction. Texto Contexto Enferm 2016;25:e2060014.
45. Watanabe S, Suemaru K, Nakanishi M, Nakajima N, Tanaka M, Tanaka A, *et al*. Assessment of the hamster cheek pouch as a model for radiation-induced oral mucositis, and evaluation of the protective effects of keratinocyte growth factor using this model. Int J Radiat Biol 2014;90:884-91.
46. Praetorius NP, Mandal TK. Alternate delivery route for amifostine as a radio-/chemo-protecting agent. J Pharm Pharmacol 2008;60:809-15.
47. Gu J, Zhu S, Li X, Wu H, Li Y, Hua F. Effect of amifostine in head and neck cancer patients treated with radiotherapy: A systematic review and meta-analysis based on randomized controlled trials. PLoS One 2014;9:e95968.