ABSTRACT:
Oral mucositis is a frequent adverse reaction of radiation therapy of head and neck malignancies. The incidence and severity of these sequelae of radiation have increased with the use of altered fractionated schedules and concurrent chemotherapy. Mucositis may confine the patient’s tolerance of antineoplastic therapy, and the nutritional status is endangered. Thus, the cancer treatment may be dramatically affected along with the patient’s quality of life. In order to prevent and treat this condition many treatment options are available, but the complete, effective prevention and therapy cannot be achieved. Research leading to a better understanding of the mechanisms of mucosal injury will ideally result in more specific, more targeted, and effective strategies for prevention of mucositis rather than current management algorithms that rely primarily on costly symptom management.

INTRODUCTION:
Radiation therapy is an important component in the management of patients with head and neck malignancies. Oral mucositis may be the first step of post radiation complication in majority of patients treated for various parts of the body. However, intensive mucositis may be encountered with radiation therapy of head and neck malignancies. Its use over the past several decades has increased as the concept of organ preservation has become prevalent, as well as a perception that the efficacy of radiation can be enhanced by the use of systemic agents.1 Mucositis, characterized by inflammation and denudation of the affected mucosa, is an inevitable and important consequence of radiotherapy to the head and neck with a mean incidence of 80%.2 It is acutely painful, adversely affecting patient’s quality of life, and can be the dose-limiting toxicity of radiotherapy regimes. When chemotherapy is given adjuvant to radiotherapy in advanced cases mucositis can be life threatening either because of reduced oral intake or superimposed infection causing septicemia and in some cases may result in termination of treatment. Patients undergoing conventional radiation therapy to the head and neck typically experience erythema and tenderness in the oral mucosa within 2 weeks of beginning therapy and often develop more severe damage to the epithelium within an additional 2 weeks.3

The management of mucositis thus has a major role in improving the patient’s quality of life without delay in the treatment due to the adverse effects of antineoplastic treatment. This paper reviews on the prevention and management strategies for oral mucositis in patients receiving radiation therapy for head and neck.

Pathophysiology
The development of mucositis is now thought to be a multistep process involving an initiation/vascular phase, an epithelial phase, a signaling/up-regulation phase, ulcerative phase and a healing phase.4,5,6

- During the inflammatory or vascular phase, the insult of chemotherapy or radiotherapy generates reactive oxygen species (ROS.) within epithelial cells, which release multiple cytokines resulting in inflammation.
- During the epithelial phase, multiple cytokines and transcription factors are up-regulated, leading to apoptosis and tissue damage.
- During the ulcerative phase, severe ulceration provides an environment for the invasion of microorganisms. This leads to an increase in the concentration of macrophages and induces a second peak in cytokine production. This phase occurs within 7 days of therapy.
- Healing phase, usually seen 12-16 days after therapy is characterized by cell proliferation and differentiation which results in restoration of the epithelium, although repair at the cellular level continues.4,5

Assessment:
The development of oral mucositis is predominantly influenced by the type of malignancy and the cytotoxic therapy administered, but patient factors
also play a role, including baseline poor oral health, existing mucosal damage, impaired immune status, and reduced salivary production. Other factors proposed but not consistently supported in clinical studies include patient age (children and older adults are at greater risk), female gender, low body mass, smoking, and poor nutritional status. Many grading scales are available for describing oral mucositis. Sonis et al have mentioned in their paper that World Health Organization Oral Toxicity Scale (WHO OTS) and the National Cancer Institute Common Toxicity Criteria scale (NCI CTC) were commonly used in clinical trials.

**Overview of WHO oral toxicity scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Subjective and objective assessments of oral mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Normal, moist mucosa</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Erythema present or absent</td>
</tr>
<tr>
<td></td>
<td>Soreness</td>
</tr>
<tr>
<td></td>
<td>No ulceration</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Erythema present or absent</td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td>Ability to tolerate solid food</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Erythema present or absent</td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td>Inability to tolerate solid food</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Erythema present or absent</td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td>Inability to tolerate oral intake</td>
</tr>
<tr>
<td></td>
<td>NCI Common Toxicity Criteria</td>
</tr>
<tr>
<td>Grade 0</td>
<td>Appearance of oral mucosa</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Normal oral mucosa</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Patchy pseudomembranous reaction</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Confluent pseudomembranous reaction</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Necrosis or deep ulceration</td>
</tr>
</tbody>
</table>

**Overview of NCI common toxicity criteria**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Appearance of oral mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Normal oral mucosa</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Erythema</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Patchy pseudomembranous reaction</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Confluent pseudomembranous reaction</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Necrosis or deep ulceration</td>
</tr>
</tbody>
</table>

**TREATMENT OPTIONS FOR RADIATION INDUCED MUCOSITIS:**

**Prophylactic measures:**

Patients who maintain their oral hygiene have less chance of suffering from oral mucositis when compared to those who do not maintain their hygiene. Adequate quality of life can be ensured by prevention, identification and early treatment of oral lesions. The following prophylactic and diagnostic steps are indicated:

a. Avoidance of wearing removable dentures, which can serve as home for microorganisms, namely Candida species, in the acute stage of mucositis. In addition, apply measures of oral hygiene involving chlorine-releasing products or chlorhexidine digluconate.

b. Use of mouthrinses without alcohol. Chlorhexidine digluconate (a broad spectrum antibacterial agent which is also active against Candida species) can be applied in solution form at concentrations of 0.12% and 0.2%. The lesser concentration is supplied as a mouthrinse, while the 0.2% presentation is used as a bioadhesive gel. Dilution of hydrogen peroxide in equal proportions of water can help clear food debris that accumulate on the teeth and mucosa.

c. Thermal or mechanical trauma can be avoided by intake of soft food at room temperature. Dental caries can be reduced by intake of low carbohydrate diet.

d. Oral mucosa can be kept moist by drinking of water.

e. Careful dental and gingival hygiene using a very soft toothbrush is indicated, provided the platelet count is over 5 x 10^9 platelets/L, avoidance of use of toothpaste above grade 1 mucositis.

f. The patient’s orthodontist should be consulted to assess the benefits of orthodontic treatment and inherent irritating actions which they may exert upon oral cavity.

**Intervention therapies:**

1. **Proliferating epithelial cell protection:**

Mucositis can be prevented by sparing the normal tissues from tumoricidal action of radiation therapy. Recently, Amifostine (WR-2721) has been advocated as a drug able to accomplish this goal. Amifostine is a phosphorylated aminothiol prodrug. In tissue, membrane-bound alkaline phosphatase dephosphorylates the drug to its active metabolite, the free thiol WR-1065. The postulated mechanism of action of WR-1065 is scavenging of free radicals created by the actions of radiation. To date, clinical studies of Amifostine as a normal tissue protector have shown efficacy protecting certain normal tissues without detriment to tumor control, although for some radioprotection of tumors still remains a concern. Bourhis and colleagues randomized 26 patients treated with an extremely accelerated course of radiation. Patients randomized to Amifostine had a lower incidence of grade 4 mucositis and...
required their feeding tubes for a shorter duration. However, the tolerance of the drug was poor. Buntzel et al investigated the role of Amifostine with concurrent chemotherapy and radiation. Randomizing 28 patients, they reported a significant reduction in mucositis because none of the patients receiving Amifostine had grade 3 or 4 mucositis compared with 86% of patients treated with radiation alone. Bourlis and colleagues postulated that it was easier to see the protective benefits of Amifostine when the acute toxicity was likely to be severe as expected with concurrent chemoradiation or very accelerated radiation. Epstein and colleagues have shown that radiation-induced mucositis appears to be modified by saliva volume and the concentration of epidermal growth factor in the oral environment. Currently, Amifostine is approved by the FDA only to reduce the severity of xerostomia after radiation therapy and to reduce renal toxicity with cisplatin chemotherapy.

b) Epidermal growth factor (EGF) is secreted in normal saliva, and its output decreases during a course of radiation. In a study 10, 50,100 µg/mL dose of EGF delivered in the form of spray reduced the incidence of severity of oral mucositis.

c) Interleukin 11 (100 µg/mL, subcutaneously) has been shown to diminish the radiosensitivity of clonogenic stem cells in hamsters through an uncertain mechanism.

Certain growth factors have also been identified as potential agents for mucositis prophylaxis.

d) Transforming growth factor inhibits cell proliferation by arresting cells in G1, a radioresistant phase of the cell cycle. A phase I study suggested a reduction in chemotherapy-induced mucositis after administration of TGF-beta3 mouthwashes (10 ml) for 4 days, four times a day, starting 1 day before chemotherapy, dose escalating in the patients from 25 µg/mL to 50 µg/mL and 100 µg/mL, but other studies in humans receiving chemotherapy have been negative with regards to transforming growth factor-B3 reducing mucositis.

e) Keratinocyte Growth factor (KGF) is another growth factor speculated to have a role in prevention of mucositis. KGF has stem cell stimulatory properties. It may increase the number of clonogens, thereby increasing the overall number of surviving clonogens, but also may modify the migration and differentiation processes. Dorr et al have described marked increase in oral mucosal radiation tolerance in mice treated with recombinant human keratinocyte growth factor (rHuKGF). Palifermin is a recombinant human KGF that belongs to Fibroblast growth factor family of cytokines. The ability of Palifermin to reduce mucositis in a clinical setting has been tested in a pivotal phase III double blind placebo-controlled trial of patients with Non-Hodgkin’s lymphoma undergoing bone marrow transplantation. Palifermin delivered prior to total body irradiation at a dose of 60mcg/kg/day for three times showed to be effective in reducing the severity of mucositis. Phase II and III trials testing KGF in patients receiving head and neck irradiation need to be performed.

I) Targeting inflammation

Radiation mucositis is associated with inflammatory reactions. But there are very few data regarding the use of classical anti-inflammatory drugs (steroids and NSAIDs) for the treatment of radiation-induced mucositis.

A) Benzydamine hydrochloride is an agent that has been studied for the prevention of radiation mucositis. The drug has numerous properties, including analgesic, antimicrobial, and anesthetic, but its primary mode of action is believed to be anti-inflammatory. BenzydamineHCl has been shown to inhibit the production and effects of inflammatory cytokines, particularly tumor necrosis factor. Benzydamine has also sparked interest as a possible agent to use for prevention of mucositis because data have shown GM-CSF can influence the proliferation of keratinocytes. This interest was further supported by observations that patients receiving GM-CSF with myeloablative chemotherapy for hematologic malignancies appeared to have a lower incidence of grade 3 and 4 mucositis compared to placebo controls.

Makkonen et al reported on 40 patients all treated with topical sucralfate who were randomized to receive GM-CSF. There was no reduction in the severity of mucositis, but there was significant toxicity in patients receiving the study drug. Topical administration of GM-CSF is also under investigation. Nicolatou et al and Rovirosa et al have reported encouraging results in single arm trials testing topical GM-CSF in patients receiving radiation for head and neck cancers.

II) Targeting inflammation

Radiation mucositis is associated with inflammatory reactions. But there are very few data regarding the use of classical anti-inflammatory drugs (steroids and NSAIDs) for the treatment of radiation-induced mucositis.

A) Benzydamine hydrochloride is an agent that has been studied for the prevention of radiation mucositis. The drug has numerous properties, including analgesic, antimicrobial, and anesthetic, but its primary mode of action is believed to be anti-inflammatory. BenzydamineHCl has been shown to inhibit the production and effects of inflammatory cytokines, particularly tumor necrosis factor. BenzydamineHCl has been shown to inhibit the production and effects of inflammatory cytokines, particularly tumor necrosis factor. BenzydamineHCl has been shown to inhibit the production and effects of inflammatory cytokines, particularly tumor necrosis factor.
Treatment Of Radiation Mucositis

A) Chlorhexidine is a broad-spectrum rinse effective against both gram-positive and gram-negative bacteria and yeast. It has been tested in several randomized trials for preventing or alleviating oral mucositis; yet no trial has shown it to be efficacious. In fact, Foote and colleagues concluded that not only was chlorhexidine not effective in preventing mucositis, it was even detrimental for their patients undergoing radiation for head and neck cancer.39 Okuno and colleagues40 found no differences in objective measures of mucositis in patients treated with a nonabsorbable antibiotic lozenge compared with patients using a placebo lozenge, but patient reported scores were better in patients treated with an active lozenge. Syronds and associates similarly tested a PTA (Polymyxin E, Tobramycin, Amphoter- icin B) pastille. There was no difference between the experimental and control arms for the study’s primary endpoint and the incidence of thick pseudem-

B) Topical prostaglandins are another group of agents believed to have anti-inflammatory properties that may benefit patients who will develop radiation-induced mucositis. Both prostaglandin E1 (misoprostol) and prostaglandin E2 (prostin) have been tested in small trials and neither have been shown to either prevent or reduce the severity of radiation-induced mucositis.32, 33

C) Azelastine is a compound that has been shown to possibly reduce the respiratory burst activity of neutrophils and reduce cytokine release from lymphocytes. It was shown to diminish the severity of oral mucositis in patients receiving radiation therapy in addition to chemotherapy for oral cancer.34

D) Saforis is a proprietary oral suspension of L-glutamine that enhances the uptake of this amino acid into epithelial cells. Glutamine role in reduction of mucosal injury was by reducing the proinflammatory cytokine production and cytokine related apoptosis.35,36 with promotion of healing via increasing fibroblast and collagen synthesis.37 In a Phase III study, this topical agent reduced the incidence of clinically significant chemotherapy-induced oral mucositis compared to placebo.38

II) Targeting infection.

Topical antimicrobials have been studied as a strategy to prevent or ameliorate the degree of mucositis. Although it is hypothesized that aerobic gram-negative bacteria are most likely responsible for exacerbating the pain and ulceration of radiation mucosal injury, a broader spectrum of antimicrobials has been tested.

A) Chlorhexidine is a broad-spectrum rinse effective against both gram-positive and gram-negative bacteria and yeast. It has been tested in several randomized trials for preventing or alleviating oral mucositis; yet no trial has shown it to be efficacious. In fact, Foote and colleagues concluded that not only was chlorhexidine not effective in preventing mucositis, it was even detrimental for their patients undergoing radiation for head and neck cancer.39 Okuno and colleagues40 found no differences in objective measures of mucositis in patients treated with a nonabsorbable antibiotic lozenge compared with patients using a placebo lozenge, but patient reported scores were better in patients treated with an active lozenge. Syronds and associates similarly tested a PTA (Polymyxin E, Tobramycin, Amphoter- icin B) pastille. There was no difference between the experimental and control arms for the study’s primary endpoint and the incidence of thick pseudem-

b}
as an intraoral dressing. In addition they may contain topical anesthetics which acts for short duration but the net function is long term coverage. Sucralfate suspension thought to hold on to ulcers of gastrointestinal mucosa forming a surface barrier and aids in the treatment of these ulcers. Taking this into account it was proposed sucralfate would also hold onto the areas of oral ulceration too. However, mixed results have been observed in clinical trials.47,48,49,50

5) Radiotherapy technique. In spite of technical advances, irradiation of non-target tissue (such as the oral cavity mucosa) remains unavoidable. The use of different sources of energy (like heavy particle) or modern three-dimensional treatment planning (Intensity Modulated Radiation Therapy) permit to better focus the dose around the target area and partially protect normal tissue like oral mucosa.46

6) RK-0202 (RkKinetix)

It consists of the antioxidant, N-acetylcysteine, in a proprietary matrix for topical application in the oral cavity. In a placebo-controlled phase II trial in patients with head and neck cancer, this agent significantly reduced the incidence of severe oral mucositis up to doses of 50-Gy radiation therapy.31

CONCLUSIONS

Oral mucositis is a serious and challenging complication of cytoreductive therapy in cancer patients. Because the treatment of mucositis is limited, prophylaxis is stressed. Patient education with regard to oral hygiene is emphasized. It's also important to assess the patient's psychological condition, in particular depressive disorders. This is important because treatments with antidepressive medication will not only contribute to lift the depression, but also to reduce the pain somatization. Although mucositis is rarely life-threatening, it will interfere, to a great extent, with the outcome of the cancer treatment.

REFERENCES


3) Duncan M, Grant G. Review article: oral and intestinal mucositis—causes and possible treatments. Aliment Pharmacol Ther 2003;18:853-874


20) Potten C: Protection of the small intestinal clonogenic
stem cells from radiation-induced damage by pretreatment with interleukin 11 also increases murine survival time. Stem Cells 1996;14:452-459.


Best scientific paper
"Oral malignancy- A threat to mankind, Fact"

DR. SEEMA V. BARKI

Best scientific paper
"Evaluation of the efficacy of Meloxicam mucoadhesive patches in dental pain reduction"

DR. MANISHA JADHAV

Best scientific paper
"Efficacy on curd on saliva secretion in comparison with pH equivalent lemon juice in healthy volunteers - An Experimental cross over study"

DR. DHANYA S. RAO

Best scientific paper
"Ultrasonography- An aid in differentiating periapical lesions"

Dr. Vidhi Vinayak
MDS- 5th Rank
May 2012 RGUHS

Dr. Shakunthala
MDS - 7th Rank
May 2012 RGUHS
Dr. BHAVANA S BAGALAD
BEST PAPER AWARD
Won 2nd place at 25th ISDR (IADR – Indian section) international conference October 2012 Chennai.

Dr. MANJIRI JOSHI
BEST PAPER AWARD
Won 2nd place at 25th ISDR (IADR – Indian section) international conference, October 2012, Chennai.

Dr. Ishu Jain – won 1st prize in paper presentation on “Management of open apex with periapical radiolucency using MTA” in 40th IDA Karnataka State Dental Conference 2012 held at Bantwal, Under the guidance of Dr. Dhanyakumar N M. Prof and Head.

Dr. Jitender Reddy – won 1st prize in paper presentation on “Who wins the game of shaping the root canal?” in 40th IDA Karnataka State Dental Conference 2012 held at Bantwal, Under the guidance of Dr. R. S. Basavanna proff.

Dr. Daaman Nagpal – won 1st prize in poster presentation on “Green Dentistry-a lost science revisited” in 40th IDA Karnataka State Dental Conference 2012 held at Bantwal, Under the guidance of Dr. Dhanyakumar N.M. proff and Head.
College of Dental Sciences, Davangere conducted a screening camp for HIV Patients at ART centre in Chigateri hospital, Davangere on 29-12-2012 in association with IDA, Davangere Branch

Republic day celebration on 26th Jan 2013

Dentist Day celebration on 6th March 2013

Guest lecture by Prof. Shakuntala Gurusiddaiah on occasion of International women's day celebrated on 8th March 2013
Felicitation of Dr. Rajendra Desai, Professor, Oral and Maxillofacial Surgery, CODS, Davangere at the AGM IDA DVG 2012

Life time achievement Doctors award in Davangere
Dr. Rajeshwari G. Annigeri
Prof. & Head
Dept. of Oral Medicine & Radiology
CODS, Davangere

Dr. Devanas G.M Asst.Prof.
Dept. of Pedodontics, CODS, Davangere
Best Hon. Secretary IDA Karnataka
40th KSDC Puttur 2012
**STAFF ACHIEVEMENTS**

**Dr. Reshma Dodwad** has been awarded as first place in Best Scientific Paper presentation 40th Karnataka State Dental Conference 2012 Nov. 30th to Dec 2nd 2012.

**Veerabahu Award Runner up**
Best local branch
66th Indian Dental Conference,
Kolkata 2013

**Dr. Sushanth V.H** Asst. Prof.
Dept. of Public Health Dentistry, CODS,
Davangere
Best CDH representative
40th KSDC, Pattur 2012

**CULTURAL ACTIVITIES OF CODS**