Treatment Of Radiation Mucositis- An Inevitable Entity

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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.1Mucositis, 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 vas¬cular phase, the insult of chemother¬apy or radiotherapy generates reactive oxygen species (ROS.) within epithelial cells, which release multiple cytokines re¬sulting in inflammation.
- During the epithelial phase, multi¬ple 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 micro-organisms. This leads to an in¬crease in the concentration of macro¬phages 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 pro¬liferation and differentiation which results in res¬toration of the epithelium, although re¬pair 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.[6,7]

Other factors proposed but not con¬sistently supported in clinical studies include patient age (children and old¬er adults are at greater risk), female gender, low body mass, smoking, and poor nutritional status.[8]

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 Can¬cer Institute Common Toxicity Crite¬ria scale (NCI CTC) were commonly used in clinical trials.[5]

Overview of WHO oral toxicity scale

Grade Subjective and objective assessments of oral mucosa

Grade 0 Normal, moist mucosa

Grade 1 Erythema present or absent

Soreness

No ulceration

Grade 2 Erythema present or absent

Ulceration

Ability to tolerate solid food

Grade 3 Erythema present or absent

Ulceration

Inability to tolerate solid food

Grade 4 Erythema presentor absent

Ulceration

Inability to tolerate oral intake

NCI Common Toxicity Criteria

Grade Appearance of oral mucosa

Grade 0 Normal oral mucosa

Grade 1 Erythema

Grade 2 Patchy pseudomembranous reaction

Grade 3 Confluent pseudomembranous reaction

Grade 4 Necrosis or deep ulceration

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.[9,10] 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.[11,12,13] 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 109 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.[14]

Intervention therapies:

I) Proliferating epithelial cell protection:

Mucositis can be prevented by sparing the normal tissues from tumoricidal action of radiation therapy.

a) Recently, Amifostine (WR-2721) has been advocated as a drug able to accomplish this goal. Amifostine is a phosphorylated aminothiol prodrug.15 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[16]. 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.[17] 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.[18] Bourhis 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.[17] 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.[19]

c) Interleukin 11 (100 µg/mL, subcutaneously) has been shown to diminish the radiosensitivity of clonogenic stem cells in hamsters through an uncertain mechanism.[20]

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. [21], but other studies in humans receiving chemotherapy have been negative with regards to transforming growth factor-B3 reducing mucositis.[22]

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).23Palifermin 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 phaseIII 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 .[24] Phase II and III trials testing KGF in patients receiving head and neck irradiation need to be performed.

f) Granulocyte macrophage colony-stimulating factor (GM-CSF), a hematopoietic growth factor, 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.25 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.26-Makkonen et al27 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 al28 and Rovirosa et al29 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 @.30 Epstein et al 31 recently reported on a randomized trial studying the efficacy of a 0.15% benzydamine rinse for the prevention of mucositis. Nearly 150 patients were randomized. The authors found that for conventionally fractionated radiation up to cumulative doses of 50 Gy, benzydamine significantly (P _ .006) reduced erythema and ulceration by approximately 30% compared with the placebo and greater than 33% of benzydamine subjects remained ulcer free compared with 18% of placebo subjects (P

_ .037). However, benzydamine was not effective in subjects receiving accelerated radiation doses.

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 evaluated 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 preduction and cytokine related apoptosis35,36 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]

III) 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 bacilli 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. Symonds and associates similarly tested a PTA(Polymyxin E, Tobramycin, Amphotericin B) pastille. There was no difference between the experimental and control arms for the study's primary endpoint and the incidence of thick pseudomembrane formation, but there were differences in several of the measured secondary endpoints including a lower incidence of worse reported grade of mucositis, dysphagia, and weight loss in patients treated with the drug. Both studies suggest that there may be an effect on reducing mucositis with topical antibiotic lozenges, but it may be small. Wijers et al41 also tested a PTA paste in a randomized placebo-controlled double-blind study and did not find that PTA reduced the incidence of mucositis.

Based on the positive findings of several of the randomized trials, a large randomized trial studying a novel broad-spectrum antimicrobial, Iseganan HCl, was conducted.42 The study randomized over 500 patients which included active rinse group, a placebo control, and a control of standard of care. There was no demonstrable benefit to active drug over placebo in reducing the incidence of grade 3 or greater mucositis, although the use of either placebo or active drug rinse decreased the incidence of severe mucositis compared with standard of care.

IV) Other approaches:

Physical agents

1) Cryotherapy:It has been proposed that during chemotherapy management, if blood flow to the oral mucosa could be decreased then the particular tissue would be exposed to a smaller amount of drug, resulting in less mucositis. This can be accomplished by having patients suck on ice chips before and during treatment and is termed cryotherapy. Cryotherapy has showed considerable results to reduce oral mucositis in patients taking 5-FU chemotherapy in two clinical trials.[43,44]

2) Low- to middle-energy laser therapy has been advocated as a therapy to promote wound healing and has been used to treat patients with chronic wounds. Additionally, low-level laser therapy appears to have anti-inflammatory and analgesic properties. In a small randomized trial of 30 patients, Bensadoun et al45 tested the efficacy of a low-energy helium-neon laser to prevent radiation-induced mucositis. The investigators reported a significant reduction in the incidence of grade 3 mucositis, as well as a significant reduction in pain in patients receiving treatment with the laser. Further investigations of this novel therapy are ongoing.

3) Silver nitrate. Silver nitrate is a caustic agent, which has been thought to reduce the severity of oral mucositis by stimulating the regeneration of oral mucosa damaged by radiation therapy.46

4) Coating Agents. The purpose of coating agent is to protect the ulceration of mucositis by functioning

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 (RxKinetix)

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.[51]

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.

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Oral Medicine & Radiology

Achievements

DR. SEEMA V. BARKI

Best scientific paper
"Oral malignancy- A threat to mankind, Fact"
National IAOMR P.G. convention-2012, Guntur.

DR. MANISHA JADHAV

Best scientific paper
" Evaluation of the efficacy ofMeloxicam mucoadhesive patches in dental painreduction"
National IAOMR P.G. convention-2012, Guntur.

Best scientific paper
"Efficacy on curd on saliva secretion in comparision with pH equivalent lemon juice in healthy volunteers – An Experimental cross over study"
P.G.Talent search, Tirupathi, Sep 14 & 15, 2012.

DR. DHANYA S. RAO

Best scientific paper
"Ultrasonography- An aid in differentiating periapical lesions"
National IAOMR P.G. convention-2012, Guntur.

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

Dr. Shakunthala
MDS - 7th Rank
May 2012 RGUHS

Oral and Maxillofacial Pathology and Microbiology

Achievements

Dr. NACHIAMMAI

BEST PAPER AWARD
Won at 1st South Zone Convention ORAMPS Sep 2012, CODS, Davangere.

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.

Conservative & Endodontics

Dr. Ishu Jain –won 1st prize in paper presentation on

" Management of open apex with periapical radiolucency using MTA"

In 40 th IDA Karnataka State Dental Conference 2012 held at Bantwal, Under the guidance of Dr. Dhanyakumar N M, Proff and Head.

Dr.Jitender Reddy - won 1st prize in paper presentation on

"Who wins the game of shaping the root canal?"

in 40 th IDA Karnataka State Dental Conference 2012 held at Bantwal, Under the guidance of Dr. R. S . Basavanna proff.

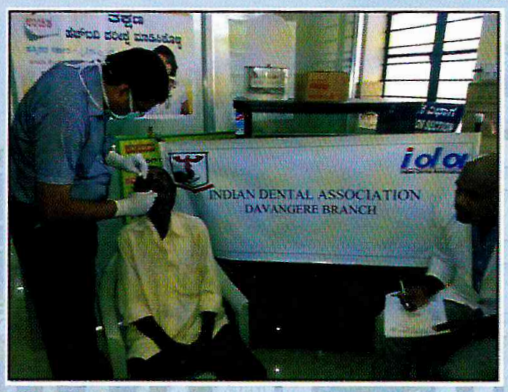
Dr. Daaman Nagpal – won 1st prize in poster presentation on

" Green Dentistry- a lost science revisited "

in 40 th IDA Karnataka State Dental Conference 2012 held at Bantwal, Under the guidance of Dr. Dhanyakumar N .M. proff and Head.

CODS ACTIVITIES

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

STAFF ACHIEVEMENTS

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. Devarasa G.M Asst.Prof.
Dept. of Pedodontics, CODS, Davangere
Best Hon. Secretary IDA Karnataka
4oth 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, Puttur 2012

CULTURAL ACTIVITES OF CODS