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Mucositis: Prevention and Management

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Introduction

Mucositis is defined as inflammation of mucosa as a result of damage to the mucosal lining. Oral erythema, ulceration, and pain are the chief characteristics. It is one of the commonest side effects of radiotherapy (RT) and/or chemotherapy (CT) and is also seen in patients receiving bone marrow transplantation. The severity and duration may vary from patient to patient and may depend on the type and dose of cancer therapeutic agents used [1].

Clinical Impact

Oral mucositis is one of the most frequent and dose-limiting side effects of RT and/or CT in patients with head and neck cancers. It is one of the leading causes of hospitalization among these patients and often involves utilization of significant medical resources. The morbidity of painful swallowing and difficulty to talk significantly affects the quality of life. Not infrequently, the symptoms and severity of mucositis call for interruption of therapy or lead to dose reduction, which may adversely affect the treatment outcomes. Also, the average cost of caring for patients with mucositis is considerably higher than for patients free of the condition [2–5]. Hence appropriate management of mucositis is of utmost medical importance.

Pathogenesis

The pathogenesis of mucositis is complex and multifactorial [6, 7]. Acute mucositis occurs due to the loss of squamous epithelial cells as a result of the injury inflicted on the mucosal stem cells and the inhibition of transit cell proliferation. This leads to a transient decrease in the number of epithelial cells. Because of the cellular proliferation from the basement membrane, the amount of mucosal cell depletion and the mucosal cell regeneration strikes a balance. As treatment progresses, cell regeneration cannot keep pace with the cell killing. Partial or complete denudation develops, which presents as patchy or confluent pseudomembranous mucositis. This can be painful and interferes with oral intake and nutrition. Although the clinical manifestations of mucositis are most conspicuous in the epithelium, the underlying endothelium, connective tissue, and the submucosal infiltrate also play important roles.

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Mucositis becomes clinically evident during the second or third week of radiation treatment and as early as 3 days after chemotherapy. The threshold for mucositis appears to be about 20 Gy of standard fractionated radiotherapy. Healing can be delayed for weeks to months based on the recovery of the mucosal stem cell. Excessive depletion can result in nonhealing and tissue necrosis. This may be a consequential late effect. Other significant late effects include mucosal scarring and reduced mucosal compliance, leading to chronic swallowing dysfunction. Compared to radiation-induced mucositis, the mucositis induced by chemotherapy is less severe and shorter (3–12 days). The use of concurrent CT with RT shortens the onset, exacerbates the severity, and prolongs the duration of mucositis [8, 9].

Grading of Mucositis

The diagnosis and grading of mucositis is based on clinical findings. The most commonly used scales are the National Cancer Institute (NCI) Common Toxicity Criteria (CTC version 4.0), the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) (Tables 29.1 and 29.2), the criteria established by the European Organisation for Research and Treatment of Cancer (EORTC), the criteria set out by the World Health Organization (WHO) in 1979 (Table 29.3), and the OM Assessment Scale (OMAS). RTOG criteria (CTCAE 3.0) are the older version. The new version [CTCAE 4.0] included the patient's perspective and symptoms. Most of the scales that are used in daily clinical practice are based on the measurement of oral symptoms, signs, and functional disturbances. None of the scales have been found to be superior to the other. However, a scale that evaluates both the observer and patient observations appears appropriate [10–14].

Figures 29.1, 29.2, and 29.3 show different grades of mucositis.

Video 29.1 shows a patient of carcinoma of the supraglottis on chemoradiotherapy, with Grade 3 mucositis.

Table 29.1 RTOG toxicity criteria [CTCAE 3.0]

Grade I	Erythema of the mucosa
Grade II	Patchy ulcerations or pseudomembranes
Grade III	Confluent ulcerations or pseudomembranes; bleeding with minor trauma
Grade IV	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
Grade V	Death

Table 29.2 RTOG toxicity criteria [CTCAE 4.0]

Grade I	Asymptomatic or mild symptoms; intervention not indicated
Grade II	Moderate pain; not interfering with oral intake; modified diet indicated
Grade III	Severe pain; interfering with oral intake
Grade IV	Life-threatening consequences; urgent
Grade V	Death

Table 29.3 WHO mucositis grading

Grade 0	No changes
Grade I	Soreness/erythema
Grade II	Soreness/erythema + ulceration + can eat solid foods
Grade III	Soreness/erythema + ulceration + can use a liquid diet only
Grade IV	Soreness/erythema + ulceration + oral alimentation is not possible

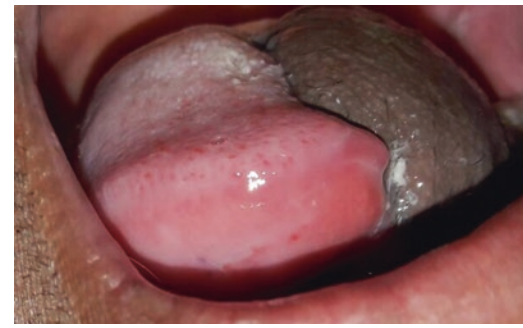

Fig. 29.1 Grade I mucositis (erythema)

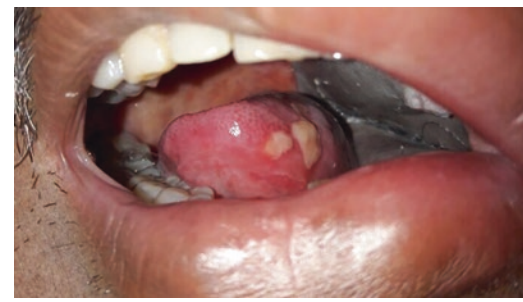

Fig. 29.2 Grade II mucositis (patchy ulcerations or pseudomembranes)

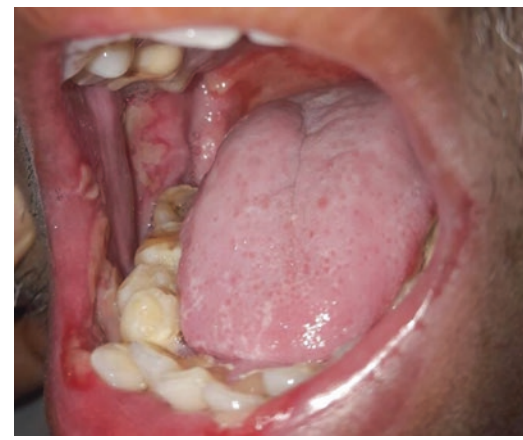

Fig. 29.3 Grade III mucositis (confluent ulcerations or pseudomembranes)

Symptoms

Clinically, the oral mucosa may initially turn whitish followed by erythema and then after a few days more by patchy fibrinous exudates and ulceration. The incidence and severity depend upon the radiation treatment volume, dose fractionation schedule, and the use of induction and/or concomitant chemotherapy. The ensuing pain and discomfort can be severe enough to interfere with eating, swallowing, and speaking. Inability to tolerate normal diet results in weight loss, malnutrition, and dehydration [15].

Risk Factors

Identifying the presence of certain risk factors, already present at the time of diagnosis, and their modification or elimination might reduce the intensity of mucositis during treatment [16, 17].

Patient-Related Risk Factors

Poor oral hygiene
Periodontal disease
Persistent alcohol and tobacco use
Xerostomia
Weight loss more than 5% in 1 month
BMI less than 18.5
Immunosuppression

Treatment-Related Risk Factors

Radiotherapy (total dose, daily fractionation, and previous RT [18]).

Chemotherapy and targeted therapy (dosage, type of drug, and timing [9, 19]).

Also, the genetic makeup of the patient and the pattern of oral microbial flora may also influence the degree of mucositis [20].

Management

Pretreatment

Oral Hygiene

All patients should be seen by a qualified dental team, and the importance of maintaining oral hygiene needs to be explained. A soft toothbrush and floss and fluoridated toothpaste should be continued lifelong. The control of the preexisting periodontal and dental disease and a pretreatment dental prophylaxis may prevent mucositis [21–24].

Radiotherapy Technique

Proper RT planning, aiming maximal sparing of the mucosa outside any planned target volume (PTV), will reduce or prevent severe mucositis [25, 26]. When intensity-modulated RT (IMRT) is used, care must be taken to restrict the total dose to the mucosa outside PTV to less than 30 Gy in 6–7 week, without compromising coverage of the PTV with the prescribed dose. Sparing of the uninvolved tongue base, pharyngeal walls, cervical constrictors, laryngeal structures, and esophagus may also decrease the intensity and extent of mucositis and associated odynophagia [27–29].

During Treatment

Oral care is an important component in mucositis management. Oral hygiene maintenance during and after radiation will significantly reduce the chance of dental complications. Oral care during radiation involves a nontraumatic brushing. A soft brush is ideal. Flossing as tolerated, and rinsing with solutions such as normal saline with sodium bicarbonate (1 L water with 1/2 teaspoon baking soda and 1/2 teaspoon salt) about 4–6 times a day is suggested [30].

Benzydamine mouthwashes have been suggested to prevent radiation-induced mucositis

receiving moderate-dose radiation therapy (up to 50 Gy) without chemotherapy. Since the beneficial effects have not been confirmed in larger trials and since there is no direct comparison with saline or bicarbonate rinses, either agent can be suggested. The use of sucralfate, chlorhexidine, and antimicrobial lozenges is not recommended [17, 31].

No mouthwash has shown superiority over saline or bicarbonate rinses in larger studies. The use of oral care products containing alcohol and with intense flavor is not recommended. Oral prostheses should be kept clean with an antimicrobial solution, and their use should be discouraged during night time and in the presence of overt oral mucositis. Patients should be reviewed at least once in a week and should be encouraged to report any further worsening of symptoms. The use of amifostine, granulocyte macrophage colony-stimulating factor, glutamine, sucralfate, chlorhexidine, povidone iodine, aloe vera, and natural honey is not recommended. Prophylactic use of antibiotics and antifungal is not recommended except in conditions like neutropenia or immunosuppression. Secondary bacterial, fungal, and viral infections should be treated with appropriate agents [17, 31–33].

Patients receiving 5FU-based chemotherapy and those receiving melphalan prior to bone marrow transplantation have shown some benefit with cryotherapy, but their use in radiation-induced mucositis is not recommended as it may interfere with the tumor control [34].

Use of recombinant keratinocyte growth factor [Palifermin] [35, 36] has shown benefit in patients with hematological malignancies receiving high-dose myeloablative chemotherapy, but no definite advantage was seen in patients receiving RT for head and neck cancers.

Low-level laser therapy [LLLT] [37] is a newer noninvasive method for the prevention and management of oral mucositis. By acting on mitochondrial respiration, it changes the production of intracellular reactive oxygen species. This can induce fibroblast proliferation, synthesis of collagen, a decreased inflammation, increased angiogenesis, and tissue repair.

There have been several positive randomized studies [38, 39] supporting the use of LLLT in the transplant setting. However, its potential growth-stimulating effect on tumor cell needs to be further studied, and hence it is not recommended in radiation-induced mucositis.

Supportive Care

Pain management is the single most important aspect of symptom control during head and neck radiation [40]. Most patients require both systemic and topical analgesics. Narcotic dose, frequency, and duration should be regularly adjusted to meet the intensity level of pain. Appropriate dysphagia support has to be provided, and patients with low BMI and those with significant weight loss should be closely monitored.

Conclusion

Mucositis is defined as inflammation of mucosa because of damage to the mucosal lining. It is characterized by oral erythema, ulceration, and pain. There are many grading systems available for mucositis. RTOG criteria and WHO classification are commonly used. Risk factors may be patient related or treatment related. Prevention of mucositis is important. There are currently no approved agents or strategies that reliably prevent RIM. The present-day policy is aimed at limiting the extent and severity of mucositis by appropriate treatment selection and actively restricting dose to critical structures, along with the use of supportive and palliative care.

Pearls

- Mucositis is a dose-limiting complication of radiotherapy and chemotherapy.
- Mucositis becomes clinically evident during the second or third week of radiation treatment and as early as 3 days after chemotherapy.
- Compared to radiation-induced mucositis, chemotherapy-induced mucositis is typically less severe and of shorter duration (3–12 days).
- Mucositis prevention strategies include optimum oral hygiene and meticulous radiotherapy planning.
- Though many pharmacological agents are tried, no conclusive data exists favoring any.
- Pain and supportive care is of paramount importance.

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