EPEC™-O

Education In Palliative And End-Of-Life Care For Oncology

Self-Study Module 3o:

Symptoms; Mucositis

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Abstract

Many symptoms and syndromes are commonly encountered in patients with cancer. This module first presents general approaches to symptom management, followed by management of the specific symptoms and syndromes, including: anorexia/cachexia, anxiety, constipation, depression, diarrhea, fatigue, insomnia, menopausal symptoms and sexual health, mucositis, nausea and vomiting, and skin problems.

Any symptom can be debilitating and prevent the patient and family from achieving goals that are important to them. As with other aspects of medicine, tailored management is based on the underlying etiology and pathophysiology. When several symptoms occur together, they can be interrelated and management can be complex.

Introduction

Oral mucositis is a common complication of both chemotherapy and radiation therapy. It is the dose-limiting toxicity of concurrent chemotherapy and radiotherapy and of accelerated and hyperfractionated radiotherapy. From the patient's perspective, mucositis is a debilitating toxicity of therapy.

Prevalence

The overall incidence of oral mucositis is approximately 40% in patients who receive standard-dose chemotherapy. (Ref. 1) However, the incidence varies with the type of medication and the doses and schedules used, and occurs in up to 100% of patients undergoing high-dose chemotherapy with hematopoietic stem cell transplantation. (Ref. 2)

Prognosis

Mucositis is generally self-limiting. The prognosis is generally good if the comorbidities such as pain, decreased oral intake, fluid deficits, and dental caries are also managed. However, mucositis has an impact on overall treatment outcomes. In patients receiving hematopoietic stem cell transplantation, mucositis is associated with an increased risk of infection and additional hospital days, days of parenteral nutrition, intravenous opioid use, and greater 100-day mortality. (Ref. 3) In general, the combination of neutropenia and mucositis increases the risk of infection.

Case

Review the case below, and keep it in mind as you progress through the module. How would you approach the assessment of this patient? What interventions might be appropriate?

P.J. is a 74-year-old man who noted enlarged lymph nodes while shaving. A T3N2M0 squamous cell cancer of the floor of his mouth was diagnosed. Combination chemotherapy with cisplatin and fluorouracil was begun, and concomitant radiotherapy was provided. Now two weeks into therapy, he says his mouth is exquisitely painful, and he cannot eat or drink.

Examination of his oral mucosa shows broad areas of erythematous, desquamated epithelium. Masticated food is noted between the teeth. A few areas of white plaque consistent with thrush are seen.

Pathophysiology

Increasing understanding of the pathophysiology of mucositis reveals it to be a complex problem that is not simply a result of injury to the basal epithelial stem cells.

Oral mucositis is caused by direct injury from radiation or chemotherapy, secondary infection, or graft versus host disease.

The pathobiology of mucositis is a multistage process including initiation, message generation, amplification of signaling, ulceration, and healing. (Ref. 4) The initiation phase is characterized by both DNA and non-DNA damage in the epithelial submucosa. The initial insult with radiation or chemotherapy triggers a cascade of biological events, many of which are mediated by the generation of reactive oxygen species. During the message generation phase, a number of transcription factors are upregulated (e.g., Nuclear factor kappa beta proteins, or NF-KB) leading to the production of proinflammatory cytokines and enzymes. The tissue injury caused by these factors is accelerated and amplified through feedback loops during the third phase, signaling/amplification. These events lead to the clinical phase of concern, ulceration. The oral bacteria which colonize the ulcer's surface potentiate the injury through the shedding of cell wall products. These products activate macrophages, stimulate cytokines, and increase the injury. The final phase, healing, occurs spontaneously and is dependent on extracellular matrix signals, which are not well understood, and epithelial cell migration, proliferation, and differentiation.

Assessment

Mucositis is a mucosal barrier injury, characterized clinically by oral erythema, ulceration, and pain following the use of known stomato-toxic therapy. (Ref. 2) The timing and location of the oral lesions help differentiate mucositis from oral infections and graft versus host disease. Oral viral infections frequently coincide with fever and are typically localized and involve keratinized mucosa of the hard palate, gingiva, and dorsal tongue. (Ref. 5) Oral ulcers secondary to graft versus host disease are seen in patients who have undergone allogeneic stem cell transplantation, and may develop after hematologic recovery. These ulcers are often lichenoid in character and may be associated with xerostomia. (Ref. 6) Chemotherapy-induced mucositis most commonly involves the soft palate, antrum of the tongue/floor of the mouth, and buccal mucosa. (Ref. 5) Chemotherapy-induced mucositis generally presents 5-7 days after treatment and resolves within 2 days to a few weeks. (Ref. 7)

While chemotherapy-induced mucositis tends to be acute, radiation-induced mucosal injury has a more chronic course. Radiation therapy-related mucositis is a function of the cumulative dose delivered. Mucositis is generally first seen after 15-20 Gy have been delivered to the mucosa. At about 30 Gy, ulcerative mucositis develops. (Ref. 8) Mucositis due to radiation typically lasts 6 weeks. (Ref. 9)

Management

The prevention of oral mucositis has been an important goal. Four theoretical approaches have been articulated. (Ref. 10)

1. Reduce mucous membrane exposure to the cytotoxic agent. Oral cryotherapy is recommended for patients receiving bolus 5-FU. (Ref. 11) Theoretically, placing ice in the mouth 5 minutes before bolus treatment with 5-FU and for 30 minutes after chemotherapy cools the oral cavity, leading to vasoconstriction and decreased oral cavity medication exposure. Randomized trials have demonstrated a 50% reduction in 5-FU-induced oral mucositis with cryotherapy. (Ref. 11) (Ref. 12) (Ref. 13) Additional studies are under way.

2. Reduce infectious and inflammatory complications. Another mechanistically based therapy is glutamine supplementation. L-glutamine may decrease treatment-induced metabolic deficiencies and promote healing. Studies of L-glutamine oral rinses for mucositis have not shown efficacy, likely due to poor absorption when administered topically. AES-14, a proprietary vehicle which enhances mucosal uptake of L-glutamine, reduced the incidence of mucositis when used as a two-to-three-times-daily oral rinse in a placebo-controlled Phase III trial in patients at risk for mucositis secondary to anthracycline-based chemotherapy. Additional studies are under way. (Ref. 14) Antimicrobials are largely used for the treatment of associated or secondary infections.

Iseganan, an analog of protegrin-I, has broad-spectrum antimicrobial activity. Early studies suggest its use reduces mucositis, though more data are needed. (Ref. 15)

3. Modify epithelial proliferative capabilities. Keratinocyte growth factor, a member of the fibroblast growth factor family, is an epithelial mitogen which acts through a subset of fibroblast growth factor receptors expressed predominantly on epithelial cells. (Ref. 7) (Ref. 16) (Ref. 17) Keratinocyte growth factor is upregulated after epithelial injury and plays a role in tissue repair. A double-blind, randomized, placebo-controlled study of the intravenous administration of recombinant human keratinocyte growth factor (rHuKGF-I, palifermin) in patients undergoing high-dose chemotherapy and hematopoietic stem cell transplantation demonstrated a reduction in the severity and duration of oral mucositis, improvement in quality of life, and decrease in opioid usage and days of total parenteral nutrition in patients who received rHuKGF-I. (Ref. 18) Additional studies are under way.

4. Reduce and inhibit proinflammatory cytokines. A topical, non-steroidal anti-inflammatory agent, benzydamine, has recently been shown to reduce the frequency and severity of oral ulcerations and the associated oral pain in patients with radiation-induced oral ulcers. (Ref. 19) Benzydamine, in addition to its analgesic and antimicrobial activities, inhibits the production and effects of proinflammatory cytokines.

Treatment

Once mucositis begins, treatment is supportive. Little has been shown to change the overall course of mucositis. General measures such as oral hygiene and dietary modification, topical local anesthetics, and systemic analgesics have been recommended. Other options are currently being studied.

Oral hygiene: Good oral hygiene appears to reduce the severity of oral mucositis. Patients should:

- Brush gently with a soft-bristled toothbrush using fluoride-containing toothpaste two or three times daily.
- Floss gently, daily, to remove food build-up.
- Rinse the mouth every 4 hours with a dilute saline and baking soda solution (½ teaspoon salt plus ½ teaspoon baking soda in a cup of warm water). While this may be soothing, it has not been formally evaluated. Chlorhexidine use is no longer recommended, as it appears no better than sterile saline. In patients with radiotherapy- related mucositis, data suggest that chlorhexidine may worsen symptoms. (Ref. 5)
- Remove dentures at night.

Limit food contact: Limit the amount of time food is allowed to come into contact with the oral mucosa. Recommend foods that require little or no chewing. Advise against foods that are irritating (e.g., acidic, spicy, salty, coarse, or dry).

Pain relief is challenging. Local anesthetics provide some pain relief. These include topical lidocaine, benzocaine, tetracaine, chirocaine, and cocaine, as well as EMLA and "magic mouthwash rinse" (a mixture of lidocaine, diphenhydramine, and magnesium/aluminum antacids). Topical analgesics that may be useful include doxepin and topical opiates such as fentanyl. In addition, mucoadherent film-forming agents such as hydroxypropylene cellulose gels, sucralfate solutions, and Gelclair may be soothing. (Ref. 20) Systemic analgesics are frequently used. Patient-controlled analgesia with an opioid is recommended. (Ref. 13) Follow standard opioid dosing guidelines (see EPEC™-O Module 2: Cancer Pain Management).

Summary

Mucositis is a mucosal barrier injury characterized by oral erythema, ulceration, and pain. Its pathobiology is a multiphase process that has only recently been described. Preventive approaches include diminishing mucosal delivery of anticancer agents, using antimicrobial/anti-inflammatory interventions, modifying the underlying pathobiology, and reducing/inhibiting proinflammatory cytokines. Once mucositis is present, treatment focuses on good oral hygiene and comfort measures.

Key Take-Home Points

1. Understanding the pathobiology of mucositis provides the opportunity to develop pathogenesis-based therapies.

2. Mucositis is a debilitating toxicity of treatment.

3. Chemotherapy produces an acute injury while the mucosal injury from radiation therapy tends to be chronic.

4. New agents for prevention are under evaluation.

5. Management focuses on symptomatic relief.

Pearls

1. To differentiate viral ulcers from treatment-induced mucositis, note that viral ulcers typically are localized and involve keratinized mucosa.

2. Oral ulcers secondary to graft versus host disease may occur after hematologic recovery.

3. Provide adequate analgesia!

4. Make a partnership with your patient and the family caregiver; draw them into the interdisciplinary team and foster their active participation in the care plan.

Pitfall

1. Using some of the old mouthwash mixes, which recent evidence suggests are actually harmful when compared in head-to-head trials. Don't use them.

References

Module 3o: Symptoms - Mucositis

1 Rosenthal C, Karthaus M, Ganser A. New strategies in the treatment and prophylaxis of chemo- and radiotherapy-induced oral mucositis. Antibiot Chemother. 2000;50:115-132. PMID: 10874460.

2 Blijlevens NMA, Donnelly JP, de Pauw BE. Mucosal barrier injury: Biology, pathology, clinical counterparts and consequences of intensive treatment for hematological malignancy: An overview. Bone Marrow Transplant. 2000;25:1269-1278. PMID: 10871732.

The pathobiology, clinical counterparts, and means of measuring MBI are discussed, together with potential approaches for prevention, amelioration and, perhaps, even cure.

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6 Woo SB, Lee SJ, Shubert MM. Graft-vs-host disease. Crit Rev Oral Biol Med. 1997;8:201-216.

7 Welte K, Reiter A, Mempel K, et al. A randomized phase III study of the efficacy of granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia. Blood. 1996;87:3143-3150. PMID: 8605328; full text.

Thirty-four patients were treated with r-metHuG-CSF. The incidence of febrile neutropenia (absolute neutrophil count <0.5 x 10(9)/L and oral temperature ≥38.5 degrees C) was 17% in children receiving r-metHuG-CSF, as compared with 40% in the control group (P=.007). Mucositis was also reduced.

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9 Plevova P. Prevention and treatment of chemotherapy and radiotherapy-induced oral mucositis: A review. Oral Oncol. 1999;35:453-470. PMID: 10694945.

Oral cooling is an inexpensive and readily available method to lower the severity of bolus 5-fluorouracil-induced oral mucositis. Results of studies with granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor are promising. Modification of the chemotherapy regimen resulting in shortening of exposition time to chemotherapy agents or chronomodulation of chemotherapy has been shown to lower mucosal toxicity of some regimens. No agent has been shown to be uniformly efficacious that can be accepted as standard therapy of chemotherapy- and radiotherapy-induced oral mucositis.

10 Wilkes JD. Prevention and treatment of oral mucositis following cancer chemotherapy. Semin Oncol. 1998;25:538-551.

The mechanisms of both direct and indirect stomatotoxicity are reviewed and efforts are made to help identify patient-related and treatment-related factors that predispose patients to oral mucositis. Various approaches to prevent and treat chemotherapy-induced mucositis are reviewed.

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Ninety-five patients scheduled to receive their first cycle of 5FU plus leucovorin were randomized to have oral cryotherapy at the time of chemotherapy administration or to serve as a control group. Subsequent mucositis was significantly reduced in the group assigned to receive cryotherapy, as judged by the attending physicians (P=.0002) and the patients themselves (P=.0001).

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A randomized, double-blind, placebo-controlled, crossover multicenter trial was conducted in breast carcinoma patients receiving at least three cycles of an anthracycline regimen. Patients developing WHO Grade (Gr) 2-4 oral mucositis during the screening cycle were randomized for crossover in two subsequent cycles.

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Twenty patients with stage IV squamous cell carcinoma of head and neck were studied. GM-CSF significantly reduced the incidence, mean duration, and mean area under the curve (AUC) of severe oral gross mucositis (grade ≥3) compared with no therapy.

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