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REVIEW ARTICLE

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Alimentary mucositis: putting the guidelines into practice

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Abstract *Background:* The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology completed an evidence-based review of the literature for the management of alimentary mucositis. *Discussion:* The present manuscript puts these guidelines into clinical practice by presenting two cases of alimentary mucositis from cancer therapy. These cases illustrate the impact of oral and gastrointestinal mucositis on patient care.

Keywords Mucositis (oral, gastrointestinal, alimentary) · Mouth · Cancer therapy · Chemotherapy · Radiotherapy · Mucosal barrier injury · Mucositis management

Introduction

The alimentary canal is susceptible to toxic effects from chemotherapy (CT) and radiotherapy (RT) for numerous cancers. These side effects of CT/RT can range from pain from oral ulceration to diarrhea because the entire alimentary tract can be affected and is often associated with extensive patient suffering. Furthermore, loss of vital mucosal barrier functions during episodes of CT/RT-induced mucositis may lead to other severe and debilitating effects such as local or disseminated infections, difficulties to eat and drink, and a need for parental nutrition and extensive narcotic analgesics. The term alimentary mucositis reflects the potential for the wide range of mucosal side effects from CT/RT.

In 2002, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) completed an evidence-based review of the literature for a variety of topics relative to the prevention and management of alimentary mucositis. Additionally, this systematic review produced guidelines that addressed terminology, mucositis scales, epidemiology, and pathogenesis of mucositis, and preventive and management strategies [1, 2]. Recently, the Mucositis Study Group has updated these guidelines and their report is being prepared for publication.

Utilizing the guidelines established by MASCC/ISOO, the goal of the present article is to demonstrate the practical use of the guidelines in clinical practice. This will be illustrated by two cases of alimentary mucositis

resulting from cancer therapy. The first case will focus on oral mucositis and the second case on gastrointestinal (GI) mucositis. We will demonstrate the impact of oral and GI mucositis on patient care and utilize the guidelines to direct treatment decisions for the prevention and management of alimentary mucositis.

Case 1 (oral mucositis): medical, social, and dental history

AB is a 48-year-old woman with a history of non-Hodgkin's lymphoma (NHL) diagnosed 2 years ago. She was initially treated with a combination of CT and localized abdominal RT. She had a relapse after 1 1/2 years of remission and was scheduled to undergo autologous hematopoietic cell transplant (auto HCT) after she was conditioned with high-dose chemotherapy (HDC) and total body irradiation (TBI).

Medical history is significant for moderate hypertension, controlled with an angiotensin-converting enzyme inhibitor, and the diagnosis of NHL. The patient has no other systemic abnormalities and is not taking any prescription or over the counter medications. She has no known allergies.

Her social history includes the following: (1) a smoking history of one pack per day for 8 years, she quit 15 years ago and (2) a history with alcohol of two glasses of wine per day, but less since her cancer diagnosis. She is married with two children and was a computer programmer for the last 5 years.

Therapy for this patient's NHL 2 years ago included CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone) and abdominal RT, which provided a complete response. Patient's toxicity history from induction of CT included a short episode of gingival bleeding, moderate localized mouth ulcers, oral pain, nausea, vomiting, diarrhea, and a 10-kg weight loss.

After the recurrence of NHL was documented, the patient was scheduled to receive an auto HCT after a regimen of myeloablative conditioning: fractionated 1,200 cGy TBI (over 4 days) followed by VP-16 (60 mg/kg) and cyclophosphamide (100 mg/kg).

At the time of the patient's pre-HCT oral examination, she reported a 2-month history of painful lower right molar with occasional jaw swelling. Her last routine dental visit was 3 years ago. An oral examination by an oral oncology specialist at the hospital dental clinic revealed deep decay in the lower right first molar that had resulted in a necrotic pulp and a periapical abscess. In addition, she was noted to have generalized gingivitis and moderate plaque. Localized moderate periodontitis was identified with a few areas of 6- to 8-mm-deep periodontal pockets with bleeding on examination.

Putting the MASCC/ISOO guidelines into practice

Foundations of oral care

What oral/dental preparation should be completed before autologous transplant?

The guidelines suggest that oral care protocol development should be interdisciplinary. Education should include staff and quality improvement processes to evaluate protocols and education.

Good oral health will help minimize the risk of local or disseminated infection from an oral source, reduce the risk of bleeding, minimize symptoms of oral pain, and reduce the impact of dry mouth symptoms. Although clinical trials are lacking to provide a clear understanding of the relationship between oral health and oral mucositis, guidance for pre-HCT dental treatment in the present case is primarily based on good clinical practice, which recommends taking steps to eliminate preexisting oral disease before HCT. The primary focus of pre-HCT dental treatment is to assess dental and periodontal health and eliminate or control active infection to eliminate potential sources of trauma and irritation for oral soft tissues and also to train patients to carry out appropriate self-care.

In the present case, 2 weeks before the start of HCT, the lower right first molar was extracted with postsurgical follow-up to ensure appropriate healing. Because of the presence of generalized gingivitis and moderate periodontitis due to inadequate oral hygiene and a build-up of calculus, the patient received careful instructions in appropriate brushing and flossing techniques. Follow-up assessments assured that the patient was successfully mastering the oral hygiene techniques. A dental cleaning was completed before HCT to remove calculus and improve gingival health. Close communication was maintained with the other disciplines involved in the patient's care to assure that pre-HCT dental treatment recommendations were followed, that treatment was provided in a timely manner, and that adequate healing of the extraction site and gingival tissues occurred by the start of transplant. The importance of maintaining optimal oral care during HCT was reinforced with the patient and her family members/care providers.

What mouth care regimens should be followed during HCT?

While the literature lacks well-designed and adequately powered clinical trials for determination of ideal mouth care regimens, there is a growing body of evidence that supports the benefits of consistently applied oral care

protocols [2, 3]. Maintaining optimal oral health to minimize oral complications such as infection, bleeding, pain, and dryness is important. An interdisciplinary team approach—nursing, medicine, and dentistry—is vital to prevent oral complications of HCT and to diagnose and manage those that do occur.

In the present case, basic oral care of tooth brushing with an ultrasoft toothbrush, bland rinses (e.g., normal saline or sodium bicarbonate rinses), mucosal moisturization and protection, and reasonable oral care strategies during HCT were recommended.

Oral mucositis scales

How is oral mucositis graded?

Numerous oral mucositis grading scales were developed over the years to score mucositis [1]. The complexity and detail of these scales varies significantly and selection of a mucositis scale is influenced by issues such as whether mucositis is being rated for reasons related to clinical care or specific oral mucositis research. The WHO mucositis scale is a relatively simple scale, which has distinct utility for routine patient care. This scale rates' overall oral status and combined mucosal appearance, symptoms, and function are described in Table 1 [4].

Mucositis epidemiology

What is the risk of developing oral mucositis for this patient?

A recent report of a clinical trial utilizing the same HDC and TBI that this patient received has reported that 98% of patients developed grade 3 or 4 mucositis [5].

What is the risk of developing GI mucositis?

The patient's risk of developing GI mucositis is almost 100%.

Generally, for HCT patients, oral mucositis frequency and severity varies significantly and depends on the aggressiveness of the conditioning regimen that is used. The incidence of any grade is near 100%, 30–50% for grade 3 or 4 oral mucositis without TBI, and >60% for grade 3 or 4 oral mucositis with TBI [1].

What are the risk factors of oral mucositis?

The risk factors of oral mucositis are the following:

- Type and dose of CT
- TBI
- Prior radiation to head and neck
- Genetics
- Graft vs host disease (GVHD) and GVHD prophylaxis.

In allogeneic HCT patients, the occurrence of oral acute GVHD or drugs used to prevent acute GVHD (methotrexate) can influence the course of mucositis [6].

Although the patient had a history of debilitating oral ulcerations with previous CT, prior mucositis history with CT is not a clear predictor of subsequent mucositis with HCT. While early occurring acute GVHD can clearly influence the course and severity of oral mucositis as can methotrexate that is used to prevent acute GVHD, these issues are not a concern in the present case because the patient is receiving an auto HCT.

What is the likely cost of getting oral mucositis?

If oral ulcerative mucositis appears during cancer therapy, an average of 5.8 additional days of narcotics and 1.9 additional days of total parenteral nutrition (TPN) will be necessary [7]. Oral mucositis is associated with increased systemic infection and increased fatigue, which will require additional supportive care needs managed by intensive nursing care, medical, and oral oncology specialists. The total cost for this additional care to manage grade 3 or 4 mucositis can be as high as $42,749 [7].

For nontransplant CT, if grade 3 or 4 mucositis occurs, 35% of patients will require dose delays, 60% will require dose reduction, and 30% will need to have CT stopped. For standard dose CT, 60% of patients with grade 3 or 4 mucositis will develop a fever and 62% will require hospitalization. In HDC, grade 3 or 4 mucositis will result in 80% of patients requiring opioid analgesics [7]. The total cost for management of grade 3 or 4 mucositis in nontransplant CT is $5,565 per cycle [8].

Table 1 WHO oral mucositis scale

Grade 0	No changes
Grade 1	Soreness/erythema
Grade 2	Soreness/erythema + ulceration + can eat solid foods
Grade 3	Soreness/erythema + ulceration + can use a liquid diet only
Grade 4	Soreness/erythema + ulceration + oral alimentation is not possible

Prevention regimens for oral mucositis

What regimens are available to prevent oral mucositis for this patient?

From the guidelines, two therapies have sufficient evidence to advocate their use to prevent mucositis. Palifermin is recommended for patients with hematological malignancies receiving HDC, TBI, and auto HCT at a dose of 60 μg/kg/day for 3 days before the conditioning treatment and for 3 days posttransplant. In addition, cryotherapy (ice chips) is recommended to prevent mucositis in patients treated with chemotherapeutic agents with very short half lives such as bolus 5-fluorouracil (5 FU) protocols, leucovorin/5 FU, etidronate, or single-dose bolus melphalan for HCT [2].

What regimens are NOT recommended to prevent oral mucositis for this patient?

From the guidelines, sufficient evidence was available not to recommend the use of two therapies. Pentoxifylline failed to prevent mucositis in patients undergoing HCT and acyclovir was ineffective in preventing mucositis in lymphoma or leukemia patients [2].

Case 1: post-HCT conditioning therapy

The patient did not receive palifermin or ice chips as a preventive therapy and developed WHO grade 2 oral mucositis 4 days posttransplant. She was able to continue brushing and flossing but recently stopped using toothpaste because of stinging. She could eat solid foods and rated her pain as 4 on a scale of 1–10 (Fig. 1).

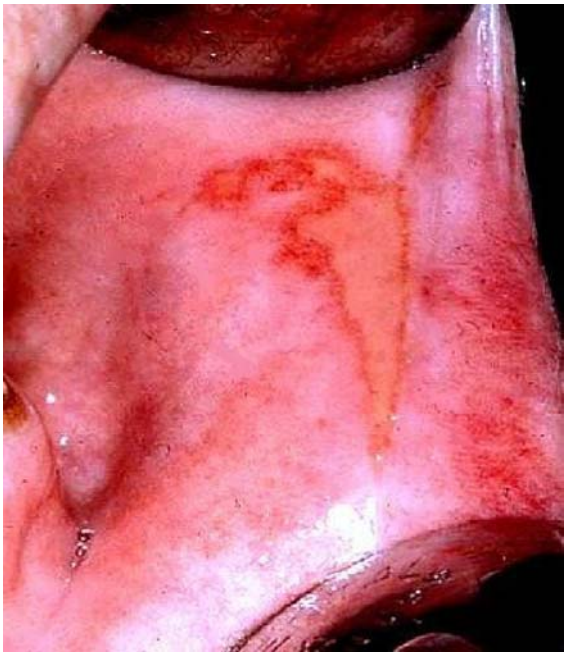

Fig. 1 Grade 2 mucositis of lower lip develops 4 days post-SCT

What management strategies should be avoided for established mucositis?

There is sufficient evidence to not recommend chlorhexidine for the management of oral mucositis. Chlorhexidine may be useful in the management of gingivitis but was not useful in the treatment of established mucositis.

The patient progressed to grade 4 oral mucositis 7 days posttransplant that lasted for approximately 4 days and then gradually resolved over the next week. She was unable to eat solid foods and rated her pain as a 10 on a scale of 1–10. (Fig. 2).

Management regimens for existing oral mucositis

How should patient's oral mucositis be managed?

A lack of well-designed clinical trials limits recommendations for symptom management of established oral mucositis. Despite the fact that there were no clinical trials to definitively establish efficacy, topical anesthetics appear to be a reasonable management option for mild/moderate and breakthrough pain management. Patients using these agents should be alert not to accidentally traumatize oral tissues while numb and not to apply anesthetics to the posterior oropharynx and risk eliminating the gag reflex and thus increase the risk of aspiration. The uses of topical agents need further evaluation.

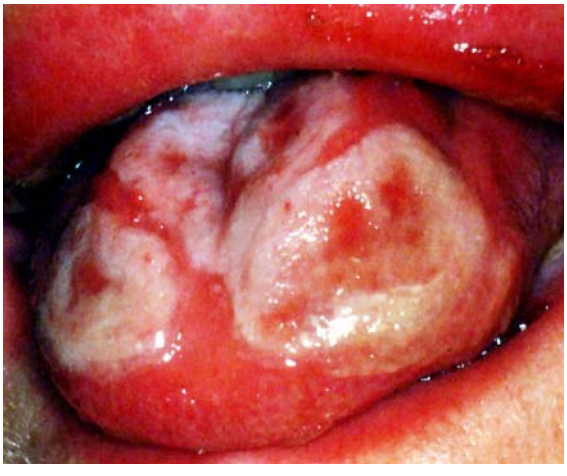

Fig. 2 Grade 4 mucositis develops 7 days post-SCT

How should this patient be managed?

The guidelines recommend that severe oral mucositis be managed through the use of patient-controlled analgesia with morphine to manage oral mucositis in patients undergoing HCT who are alert and able to operate the computerized pump. When patients are not able to operate the computerized pump, more conventional means of administering opioids is usually required but there is a lack of evidence to support the recommendation of other management regimens for oral mucositis.

Impact of nutrition from oral mucositis

What is the relationship of malnutrition to mucositis?

Grades 3 and 4 oral mucositis will reduce or prevent the ability to provide oral nutritional intake and can increase the risk of malnutrition. With standard dose CT, 70% of patients with grade 3 or 4 oral mucositis will require nutritional support by means of feeding tubes or total potential nutrition to maintain adequate nutrition [1]. With HCT, 87% of patients with grade 3 or 4 oral mucositis will require nutritional supportive efforts [1].

How should nutrition be maintained?

Recommendations regarding specific nutritional intake guidelines are available in the literature [9–11]. While practices vary considerably between transplant centers, there is evidence to support that naso-gastric feeding, when possible, is often preferable to TPN due to less cost, its ability to stimulate the GI mucosa, and a lower complication rate [9–11]. However, in cases of severe GI mucositis, TPN can be the only alternative.

Case 2 (GI mucositis): medical and social history

FG is a 56-year-old man diagnosed with Dukes' C colon cancer 8 years ago. He was treated with a sigmoid colectomy and then the CT regimen of 5 FU and folinic acid (FA).

At diagnosis, his medical history was significant for stress-induced reflux. Other than ranitidine for his reflux, he was taking no medication and had no medication or environmental allergies. Social history included the following: he was a nonsmoker, drank one half bottle of wine per day, and ran a small business. The patient was divorced with three children. His family history was significant for lung cancer and coronary artery disease and his parents are deceased.

Following colectomy, the patient was planned to receive six cycles of the Mayo regimen: 5 FU 375 mg/m^2/day and FA 20 mg/m^2/day D1–5, q28. By day 5 of cycle 1, the patient experienced diarrhea with six stools per day and worsening epigastric pain. An abdominal radiograph showed an edematous bowel wall, multiple distended bowel loops, and air-fluid levels.

Putting the MASCC/ISOO guidelines into practice

GI mucositis scales

How is diarrhea graded?

Assessment scales for GI mucositis are not as well developed as for oral mucositis. The most commonly used one is the National Cancer Institute (NCI) common toxicity criteria (CTC) for diarrhea [12] shown in Table 2. However, it should be noted that the measurement of GI toxicity is made more difficult than measuring oral toxicity due to the problems of viewing the mucosa and localizing symptoms to the affected area of the GI tract. Grading of other GI symptoms such as pain can also be performed.

How is epigastric pain graded?

Again, the most commonly used scale is the NCI/CTC dyspepsia/heartburn scale where grade 1 = mild, 2 = moderate, and 3 = severe (there is no grade 4) [12].

GI mucositis epidemiology

What is the diagnosis of the patient's GI symptoms?

The patient's symptoms are consistent with GI mucositis with NCI/CTC grade 2 diarrhea.

What are his risk factors for GI mucositis?

The patient's risk factors for GI mucositis are not well characterized but he has a history of reflux disease and he was receiving CT. In other people, RT may add to the risk of GI mucositis, as might underlying GI disease. It is also likely there are as yet, unrecognized genetic factors.

Table 2 NCI/CTC common toxicity criteria

Grade 1	Increase of less than four stools per day during pretreatment
Grade 2	Increase of four to six stools per day or nocturnal stools
Grade 3	Increase of seven or more stools per day, or incontinence, or need for parenteral support for dehydration
Grade 4	Requiring intensive care or hemodynamic collapse

Management of GI mucositis

What do the guidelines tell us about treating this patient's diarrhea?

The following therapies have sufficient evidence to advocate their use for the treatment of diarrhea: loperamide, removal of exacerbating foods from the diet and if loperamide fails, octreotide. Loperamide is a nonanalgesic opioid that slows down gut motility and is used extensively for CT- and RT-induced diarrhea. Many patients with CT-induced diarrhea develop transient lactose intolerance due to a loss of brush border enzymes so that reducing dairy intake may reduce symptoms. In the event that these strategies do not work, octreotide, a synthetic somatostatin analogue, was shown to decrease fluid secretion into the bowel and hence to reduce diarrhea [2].

What do the guidelines tell us about treating this patient's epigastric pain?

Ranitidine and omeprazole are recommended for the treatment of epigastric pain. Two studies published by Sartori et al. [13, 14] showed that omeprazole and ranitidine reduced epigastric pain and decreased gastric and duodenal erosions.

How should patient's GI mucositis be managed for the next CT cycle?

The guidelines support the continued use of ranitidine or omeprazole throughout the CT cycles because these are very inexpensive drugs. Loperamide should be added at the first evidence of diarrhea symptoms. The patient should continue to avoid exacerbating food. If the diarrhea worsens despite following these recommendations, then a CT dose reduction and/or delay should be considered.

Case 2: recurrence 4 years after initial CT utilization of guidelines

The patient returned 4 years post-CT with newly diagnosed liver metastases. He was treated with capecitabine (1.25 g/m^2 b.i.d. D1–14 q 21 days) and restarted on omeprazole with no complications of esophagitis. He did, however, have major toxicities of diarrhea and hand–foot syndrome. After a 25% dose reduction, the toxicities were manageable with loperamide and pyridoxine.

Ten months later, the patient's liver metastases progressed and his treatment was switched to FOLFOX (5 FU, FA, and oxaliplatin). His diarrhea was controlled with loperamide. The patient had a good response and treatment was stopped after six cycles (12 doses).

One year later, progressive disease returned and he was treated with single agent irinotecan. Omeprazole was continued, premedication with atropine was given, and loperamide was given at the first evidence of diarrhea. Despite this therapy, grade 4 diarrhea developed and the patient was hospitalized for diarrhea, fever, weight-loss, and cramping abdominal pain, the so-called "gastrointestinal syndrome" [15].

His diarrhea persisted despite maximum dose of loperamide (11 per day) and the patient became neutropenic. Abdominal X-ray showed edematous bowel wall, multiple distended bowel loops, and air-fluid levels. The patient was treated with intravenous fluids, antibiotics, loperamide, octreotide, granulocyte colony-stimulating factor, and morphine. He made a very slow recovery, pointing to the importance of discovering better treatment options for GI mucositis. While the gastrointestinal syndrome is more common with irinotecan due to its particular propensity for GI toxicity, it can be seen with other agents and constitutes an oncological emergency requiring immediate hospitalization and the institution of intravenous fluids and antibiotics.

Summary

These cases point to a number of important considerations in utilizing the MASCC/ISOO guidelines for patient care. First, it is vital to review institutional protocols with the guidelines in hand, questioning everything in them and ensuring that current treatment regimens are not unnecessary or even detrimental. Although some prevention and management strategies for alimentary mucositis are advocated by the MASCC/ISOO guidelines, few options are available. This limited evidence points to the importance of further research in pathophysiology, epidemiology, and therapy for alimentary mucositis. Epidemiological and clinical research into risk factors and burden of care and clinical studies of newer, more promising agents are vital to improve the management of this common and debilitating toxic side effect of cancer therapies.

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