The Oncologist
Physician Education

Mucositis: Its Occurrence, Consequences, and Treatment in the Oncology Setting

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INTRODUCTION

Mucositis induced by antineoplastic drugs is an important, dose-limiting, and costly side effect of cancer therapy. The ulcerative lesions produced by mucotoxic chemoradiotherapy are painful, restrict oral intake and, importantly, act as sites of secondary infection and portals of entry for the endogenous oral flora [1]. The overall frequency of mucositis varies and is influenced by the patient's diagnosis, age, level of oral health, and type, dose, and frequency of drug administration [2]. Some degree of mucositis occurs in approximately 40% of patients who receive cancer chemotherapy [2]. Approximately one-half of those individuals develop lesions of such severity as to require modification of their cancer treatment and/or parenteral analgesia. The condition's incidence is consistently higher among patients undergoing conditioning therapy for bone marrow/peripheral blood progenitor cell transplantation, continuous infusion therapy for breast and colon cancer, and therapy for tumors of the head and neck associating concomitant chemotherapy and radiotherapy. Among patients in the high-risk protocols, severe mucositis occurs with a frequency in excess of 60% [3-5].

Concomitant with mucositis is often a chemotherapy-induced myelosuppression. The neutropenia that results puts the patient with oral mucositis at significant risk for systemic infection. Patients with mucositis and neutropenia have a relative risk of septicemia that is greater than four times that of individuals without mucositis [6].

The morbidity of all mucositis can be profound. It is estimated that approximately 15% of patients treated with radical radiotherapy to the oral cavity and oral pharynx will require hospitalization for treatment-related complications [7]. In addition, severe oral mucositis may interfere with the ability to deliver the intended course of therapy, leading to significant interruptions in treatment, and possibly impacting on local tumor control and patient survival. It is also not unusual for mucositis to necessitate delays in cancer chemotherapy particularly with those agents that are known to be mucotoxic, including 5-fluorouracil with or without folinic acid, methotrexate, doxorubicin, etoposide, melphalan, cytosine arabinoside and cyclophosphamide.

In addition to its impact on a patient's treatment course, on quality of life, and morbidity and mortality, mucositis can also have a significant economic cost. This is particularly true in the autologous and allogeneic bone marrow transplant settings for hematologic malignancies, where the length of hospital stay may be prolonged due to severe mucositis [8].

ETIOLOGY/PATHOPHYSIOLOGY OF MUCOSITIS

Direct Mucotoxicity

It is generally accepted that oral mucositis results from the direct inhibitory effects of chemoradiotherapy on DNA replication and mucosal cell proliferation, resulting in a reduction in the renewal capabilities of the basal epithelium (Fig. 1). These events are believed to result in mucosal atrophy, collagen breakdown, and eventual ulceration [9, 10]. The high rate of cellular replication makes the oral and lower gastrointestinal mucosa particularly susceptible to this cytotoxicity [11].

Clinically, the direct mucotoxic effects of chemotherapy on the oral mucosa begin shortly after therapy has begun, and peak in severity approximately day 7 or day 10

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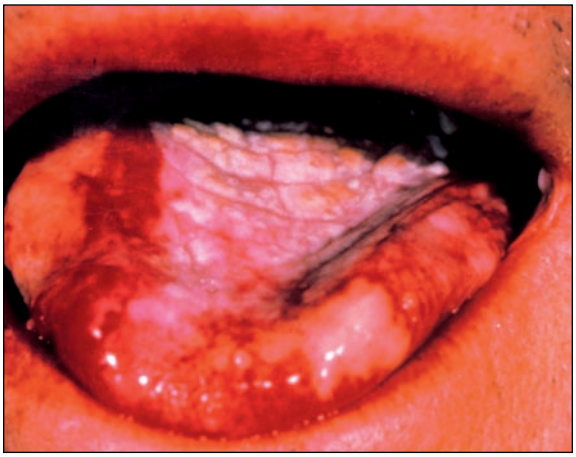

Figure 1. Oral mucositis. *Courtesy of Amgen Inc., Thousand Oaks, California.*

of therapy, with eventual resolution occurring within two weeks. Once lesions develop, they heal more quickly in the younger population.

Analyses of mucositis have largely been based on observational data. While there have been suggestions as to the mechanisms whereby mucositis develops, for the most part the complete pathophysiology of the condition is largely undefined. A detailed hypothesis has been proposed as to the mechanisms by which mucositis develops and heals and it is based on animal and clinical data, but remains somewhat speculative [12-14]. Mucositis is assumed to be a four-phase biologic process which involves an inflammatory/vascular phase, an epithelial phase, an ulcerative/microbiological phase, and a healing phase (Table 1).

Each phase is proposed to be independent and is a consequence of a series of actions mediated by cytokines and other growth factors, the direct effect of the chemotherapeutic drug on the epithelium, the oral bacterial flora, and the status of the patient's bone marrow.

The initial phase is due to the effect of chemoradiotherapy in causing the release of cytokines (e.g., interleukin 1 [IL-1]) from the epithelium and the connective tissues [12]. Cytokines such as tumor necrosis factor and IL-1 can incite an inflammatory response that may result in increased subepithelial vascularity. This phase is considered to be relatively acute.

The epithelial phase is likely the best documented, specifically for those agents that are known to impact dividing cells of the oral mucosal epithelium (those drugs which target DNA synthesis, the S phase of the cell cycle). The epithelial phase may be most profound in terms of production of ulcerative lesions. Therefore, antimetabolites that are cell-cycle specific are more mucotoxic than drugs that are cell-cycle nonspecific. This is supported by the observation that temporarily taking basal cells out of cycle appears to be mucoprotective, as does modification of apoptotic cell death [13, 14]. The epithelial phase is therefore categorized by a reduction of epithelial renewal which results in atrophy and typically begins about four to five days after chemoradiotherapy administration.

The ulcerative phase is likely the most symptomatic and biologically complex of all four phases. It is at this time which mucositis has the greatest impact on the patient's well being, as he or she is now susceptible to infection. As previously described, the occurrence of breakdown in mucosal barriers occurs concurrent with neutropenia, thereby putting the patient at risk of infection through lesions in the oral cavity.

The final hypothesized phase of mucositis regards healing which includes elements related to cell proliferation and differentiation, a return to normal of peripheral blood cell counts and control of the oral bacterial flora. The speed at which this phase takes place directly affects the duration of the mucositis condition, but likely not the peak of intensity experienced by the patient.

Indirect Mucotoxicity: Oral Infections

As part of the ulcerative/microbiological phase, the myelosuppression and inflammation that lead to the breakdown of the mucosal barriers, thereby comprising the ability of the patient to resist entry of pathogens, renders them susceptible to infection from a number of different sources, including viral, fungal, and bacterial infections. After chemotherapy, the

Table 1. The four phases of the biologic process of mucositis

Phase	Cause
Inflammatory/vascular	Due to the effect of chemoradiation in causing the release of inflammatory cytokines from the epithelium and the connective tissues. This phase is relatively acute.
Epithelial	Due to cytotoxic agents that target DNA synthesis of the oral mucosal epithelium. This phase is usually the most profound in terms of production of ulcerative lesions.
Ulcerative/microbiological	Due to breakdown in mucosal barriers. Most symptomatic and biologically complex of the phases. This phase has the greatest impact on patients' well-being and risk of infection.
Healing	Due to renewed cell proliferation and differentiation, return to normal peripheral blood counts, and control of oral bacterial flora. The speed at which this phase takes place directly affects the duration of the mucositis condition.

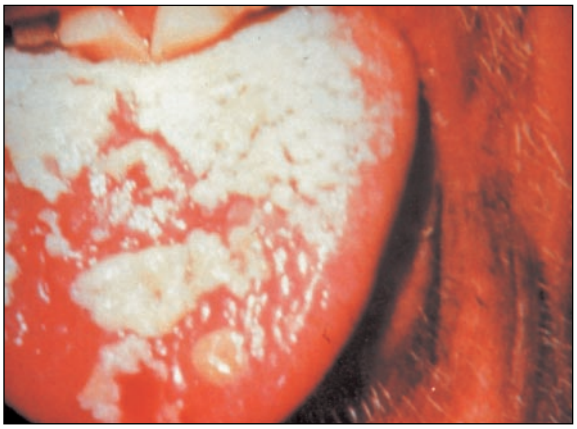

Figure 2. Candidiasis. *Courtesy of Amgen Inc., Thousand Oaks, California.*

oral cavity may be secondarily infected by a number of viral pathogens, including herpes simplex virus (HSV). Oral HSV is an extremely common infection in the general population, and in patients who develop mucositis after chemotherapy, 40% to 70% of cultures from oral lesions will demonstrate HSV [15]. Superficial fungal infections with *Candida albicans* can occur frequently in patients receiving chemoradiotherapy (Fig. 2). It has been reported that 60% to 90% of patients with cancer will have positive cultures for *Candida* species [16]. The most common organisms involved in oral bacterial superinfections include gram negative rods and anaerobes. The polymicrobial nature of the oral flora makes identification of bacterial super infections challenging.

Toxicity Scales

A major hurdle for researchers investigating mucositis has been a lack of a definitive technique to appropriately measure oral mucositis. Over the last 20 years many instruments have been developed in the literature to document and quantify changes in the tissues of the oral cavity all in oral function during and after cancer treatment. These vary from the simple 3 or 4 point "toxicity scales" to detailed and specific inventories of mucosal events and changes scored for different anatomical regions of the mouth [17]. There are a number of practical considerations to be addressed by investigators before selecting a mucositis scale: Why is mucositis being scored; who will be scoring the changes, and how often will mucositis be scored and under what "clinical" conditions?

A good scoring system must fulfill two criteria: content and validity, and inter-user/intra-user reliability. Traditionally the first criterion has been fulfilled by reviewing the relevant literature and soliciting the opinions and ideas of experts in the field. The second criterion is satisfied by demonstrating the reproducibility of the scoring system when used by the same person and/or by different individuals over a defined period of time. A list of the more commonly used mucositis scoring systems includes the scoring system proposed by the World Health Organization (WHO) (Table 2), the National Cancer Institute, the Radiation Therapy Oncology Group, and the National Cancer Institute of Canada Clinical Trials Group.

Table 2. WHO rating scale of oral toxicity

Grade	Symptom
0	No symptom
1	Soreness and erythema
2	Erythema, ulcers; can eat solid food
3	Ulcers, requires liquid diet only
4	No possible alimentation

The same descriptive terms are used in all of the scales. However, there are subtle differences which preclude interchangeably. For example, the symptom of pain, if it is included in the grading system at all, is described using terms such as "mild, moderate or severe," or as "requiring analgesics or requiring narcotics." The variations between scales also exist in the assessment of the impact of mucositis on the patient's ability to eat. A lack of agreement also exists regarding the score attached to a specific sign or symptom complex. All of these factors contribute to making comparisons between the scales difficult. Another factor limiting direct comparisons between scoring systems is the terminology used to describe signs of mucositis; for example, "mucosal denudation" versus "spotted or confluent mucositis" versus "ulcer." Generally, little information exists regarding validation of these toxicity scales [18].

It may be difficult to design one single scale for measuring mucositis that will be appropriate in all clinical situations, given the diversity of chemoradiotherapy treatments available and their resulting toxicities. However, with the advent of new forms of treatment and greater emphasis on assessment of treatment-related morbidity and mortality, there exists a strong need for universally accepted, validated scales to assess mucositis.

In summary, examples of general or overall rating scales that provide simple 0 to 3 or 0 to 4 mucositis scores which are based on clinical impressions (e.g., the WHO oral mucositis scale) are limited. In contrast, scales have been developed that combine detailed mucosal change descriptors with various subjective (e.g., pain) and performance criteria (e.g., speaking, swallowing). The oral assessment guide developed by *Eilers et al*. [19] consists of eight categories—voice, swallow, lips, tongue, saliva, mucous membranes, gingiva, and tooth—that are rated using a 1 (normal) to 3 (definitively compromised) scale. These more detailed scales have received less

experience in the clinical trial setting and frequently require the training of specialized oral cavity experts to provide consistency in mucositis assessment.

Predictive Indices/Risk Factors

Patient-Related Risks

A variety of patient-related factors appears to increase the potential for developing mucositis after chemoradiotherapy, including the age of the patient, nutritional status, type of malignancy, pretreatment oral condition, oral care during treatment, and pretreatment neutrophil counts. There are conflicting data relating to the effects of age and the development of chemotherapy-induced mucositis [20]. In general, younger patients appear to have an increased risk of chemotherapy-induced mucositis. This observation may be explained by the more rapid epithelial mitotic rate or the presence of more epidermal growth factor receptors in the epithelium of younger patients. Alternatively, the physiologic decline in renal function associated with aging may result in older patients being at higher risk of chemotherapy-induced mucositis. Hematologic malignancies are relatively more frequent in children than adults, and their treatments tend to produce more prolonged and intense myelosuppression, which may also result in more severe indirect mucotoxicity.

Other patient-related factors include chronic periodontal disease, pretreatment xerostomia which may contribute significantly to the development of oral mucositis, and any decrease in neutrophil count before chemotherapy. The latter may result in an impaired ability to mount an adequate inflammatory response to the cytotoxic effects of chemotherapy on the oral mucosa.

Therapy-Related Risks

In conjunction with patient-related factors, factors that are treatment-related include specific chemotherapeutic drug, dose, schedule, and use of radiation therapy [21]. All of these will affect the subsequent development (severity and duration) of mucositis. Protracted infusions of antimetabolites, as well as concomitant use of radiation, result in more severe mucositis [22]. Certain chemotherapeutic agents such as methotrexate and etoposide may also be secreted in the saliva, leading to increased direct mucotoxicity.

Risks are summarized in Table 3.

Prevention and Prophylaxis

Many traditional treatments are ineffective. The basic principles of mouth care—to relieve pain, prevent dehydration, provide adequate nutrition, and deal with any focus of infection such as obvious candidiasis—stand the test of time. Approaches to the prevention of mucositis induced by chemoradiotherapy can be divided into three broad categories: A) alteration of the mucosal delivery and excretion of individual chemotherapeutic agents; B) modification of the epithelial proliferative capabilities of the mucosa, and C) alteration of the potential for infections of inflammatory complications.

Some mucosal pharmacologic alterations that have been tried include cryotherapy [20, 23], allopurinol [24], propantheline [25], and pilocarpine [22]. The results have generally been mixed, but the studies have been pilot ones in a small number of patients, so conclusions are hard to draw.

Mucosal Proliferation Modifiers

It has been suggested that the rate of basal epithelial cell proliferation correlates with susceptibility with mucosal tissues with the toxic effects of chemotherapy [26]. Therefore, investigators have studied various agents that impact epithelial proliferation to identify a means of preventing chemotherapy-induced mucositis, including beta-carotene, glutamine, cytokines, dinoprostone, and silver nitrate. Preliminary results with many cytokines have been presented in the literature; however, to date, none of them have proven themselves in randomized, double-blind, placebo-controlled, registration trials [22].

Anti-Microbial/Anti-Inflammatory Approaches

Clinical trials have established that a combination of correction of existing oral conditions before therapy and aggressive mouth care can reduce the incidence and severity of oral mucositis following chemotherapy [27]. In addition to appropriate oral hygiene, trials investigating oral antimicrobial agents for the prevention of chemotherapy-induced mucositis have provided conflicting data. Studies conducted with lozenges composed of polymyxin B, Tobramycin, and amphotericin B provide some benefit in mucositis prevention in patients receiving head and neck irradiation.

Table 3. Risk factors for mucositis

Patient-Related Factors

- Type of malignancy: hematologic malignancies pose greater risk than solid tumors.
- Patients <20 years of age are at greater risk.
- Poor oral health (e.g., pre-existing periodontal disease) puts a patient at greater risk.

Therapy-Related Factors

- Chemotherapy agent used (e.g., antimetabolites).
- Dose of drug or radiation.
- Concomitant therapy.
- Radiation therapy involving the head and neck.

However, these data require confirmation. Finally, steroid mouthwashes have not been formally investigated for the prevention of chemotherapy-induced mucositis. The ability of corticosteroids to inhibit prostaglandin synthesis, combined with data from small uncontrolled trials in patients receiving radiation, does provide a hypothesis for further study of these agents [22].

In summary, the management of established mucositis can be difficult for both the patient and the provider. General approaches include effective oral care, dietary modifications and topical mucosal protectants. In addition, appropriate use of topical anesthetics and systemic analgesics remain the cornerstone of therapy. Promising agents that accelerate mucosal healing and alter the course of the biologic process of mucositis are under investigation, like the keratinocyte growth factor [28]. The use of such agents in many settings, including head and neck cancer and bone marrow transplantation, promises to substantially reduce treatment-related morbidity, improve patient quality of life, and potentially allow treatment intensification in high-risk disease.

ACKNOWLEDGMENT

Robert Heard, Ph.D., assisted with the writing of this manuscript.

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