

Oral Mucositis and Stomatitis Associated with Conventional and Targeted Anticancer Therapy

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Abstract

Oral mucositis and stomatitis are characterized by pain, inflammation, and redness in the oral cavity. In the case of mucositis, ulceration also occurs. Despite being understudied, these symptoms are some of the most troubling, and yet common, adverse effects associated with cancer treatment. The incidence of these toxicities is highly variable depending on treatment-related and patient-related risk factors. However, most cancer treatment regimens carry some risk of this toxicity. The presence of mucositis or stomatitis can result in a significant decrease in the patient's quality of life due to severe pain and the inability to eat or drink. These toxicities can also negatively affect the overall outcome of cancer treatment, leading to dose reductions and delays in treatment. Although the mechanism is not yet understood, the rapid increase in the number of targeted anticancer therapies available on the market has increased the number of patients who experience oral toxicities. The toxicities caused by targeted agents are less severe than those caused by conventional anticancer agents, but due to prolonged dosing schedules, they can still lead to significant declines in quality of life. The pathobiology of oral mucositis is a complex five phase process. It involves injury, activation of enzymes and transcription factors, upregulation of cytokine genes, inflammation/damage to tissue, and healing. These processes not only involve cells in the oral mucosa, but also the surrounding fibroblasts and connective tissue cells. A better understanding of the mechanisms behind oral mucositis and stomatitis will facilitate the development of effective prediction, prevention, and treatment strategies.

Keywords: Oral mucositis; Stomatitis; Oral toxicities; Chemotherapy; Targeted cancer therapy

Introduction

It is indisputable that the effective treatment of malignancies is often limited by the harm inflicted on normal, healthy cells [1]. Given their high rate of turnover, mucosal cells in the oral cavity are highly susceptible to the toxic effects of cancer treatment [2]. Toxicities of the oral cavity, which include mucositis and stomatitis, are some of the most significant and unavoidable toxicities associated with cancer treatment [3]. Advances in the ability of anticancer treatment to damage and kill cancer cells has also led to changes in the incidence, nature, and severity of oral complications [3]. Cytotoxic chemotherapy has long been associated with a high risk of oral toxicity. However, the risk associated with the newer targeted agents is only begun to be realized. Despite being underreported and often under recognized, oral toxicities have a tremendous impact on the cancer patient and on the resources of the healthcare system. For example, oral toxicities are a common cause of dose delays and interruptions of cancer therapy [4]. Unfortunately, the currently available treatments for oral toxicities are primarily palliative and in many cases, only marginally effective [5-7]. The lack of effective treatments and prevention strategies may be attributed to the fact that research on oral toxicities has lagged behind research on other chemotherapy and radiation-related toxicities such as febrile neutropenia and nausea and vomiting [4].

Mucositis and Stomatitis

The damage inflicted upon the oral cavity by various modalities of cancer treatment can result in a variety of conditions including

Grade 1	Oral soreness, erythema
Grade 2	Ulcers, but able to eat solid food
Grade 3	Oral ulcers and able to take liquids only
Grade 4	Oral alimentation impossible

Table 1: World Health Organization Oral Mucositis Scale adapted from [4,10]

oral mucositis and stomatitis. Clinically, the terms mucositis and stomatitis are often used interchangeably, but they do not have identical pathologies [2].

Mucositis is the term describing the lesions caused by anticancer agents. It can occur to any mucosal cells, but most commonly occurs in the cells of the oral cavity and small intestine [5]. Oral mucositis caused by cytotoxic chemotherapy is characterized by painful inflammation, erythema, swelling, and ulcerations of the oral mucosa in the oral cavity, oropharynx, and hypopharynx [8,9]. Oral mucositis varies in intensity from a grade 1 to a grade 4. Grade 1 is characterized by redness and soreness and grade 4 prevents the patient from ingesting anything orally (Table 1) [10].

Stomatitis refers to inflammation that occurs in any tissue in the oral cavity [9]. Therefore, stomatitis includes a broad range of conditions, including oral mucositis. A majority of the research performed to date has specifically focused on oral mucositis. However, the increasing use of targeted anticancer agents (e.g. mammalian target of rapamycin (mTOR) inhibitors, inhibitors of Epidermal Growth Factor Receptor (EGFR) signaling, and tyrosine kinase inhibitors) has brought forth the need to carefully distinguish between the pathology and pathogenesis of mucositis and stomatitis.

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Treatment-related	Patient-related
• Type of medication	• Type of malignancy
• Dose	• Age
• Schedule of medication (e.g. number of cycles)	• Poor oral health and hygiene
• Route of administration	• Salivary gland dysfunction
• Concomitant radiation therapy	• Body mass index
• Dose and field of radiation	• Gender
	• Genetic polymorphisms in drug metabolizing enzymes [22] and TNF- α [21]
	• Co-morbid disease states (e.g. psoriasis, Addison's disease, diabetes) [6]

Table 2: Risk factors for oral mucositis adapted from [9,20].

Epidemiology of Oral Mucositis

The incidence and severity of mucositis is highly variable and is dependent on treatment-related and patient-related risk factors [11] (Table 2). Currently, treatment-related risk factors are more important to consider than patient-related factors, and should be assessed before treatment initiation [4]. Treatment-related risk factors include type, dose, schedule of chemotherapy, route of administration, and concomitant use of chemotherapy and radiation [9,12]. Patients who receive standard-dose chemotherapy has an estimated 40% risk of all-grade mucositis [13] and the risk of mucositis approaches 100% in patients with head and neck cancer who receive both intensive chemotherapy and radiation [4,14]. The overall risk of developing mucositis and the severity of mucositis positively correlate with the number of chemotherapy cycles due to increased exposure and the cumulative damage caused by anticancer agents [3,4].

The reported incidence of mucositis is striking. However, it is likely what the true incidence of mucositis in clinical practice is much higher. Currently available knowledge on oral mucositis is derived from clinical trials. Unfortunately, relatively few clinical trials have focused on mucositis as a specific outcome and clinical trials often do not include the full range of patients (e.g. elderly patients, patients with comorbidities, non-adherent patients) [4]. Additionally, mucositis often emerges between treatment cycles when clinical monitoring is sporadic [15].

Although it is difficult to predict whether a patient will develop mucositis solely based on the class of drug dispensed [2], there are several drugs that are associated with an increased propensity to damage the oral mucosa. These drugs include methotrexate, doxorubicin, 5-fluorouracil, busulfan, bleomycin, cisplatin, carboplatin, mTOR inhibitors, inhibitors of EGFR signaling, and selected tyrosine kinase inhibitors [2,4,8,16-19].

Most research has focused on treatment-related risk factors, given the variable response of individual patients to the same treatment regimen. However, patient-related risk factors also play an important role in oral toxicity risk [4]. Currently, data is inconclusive pertaining to the influence of age, gender, body mass index, and nutritional status on chemotherapy-induced mucositis [4,20]. However, the impact of genetic factors has become unmistakable. Importantly, differences in the expression of genes associated with the pathogenesis of mucositis are common [9]. For example, polymorphisms in the tumor necrosis factor genes have been shown to increase the risk of toxic lesions [21]. Additionally, although relatively rare, deficiencies in drug metabolizing enzymes due to genetic polymorphisms have been associated with an increased risk of methotrexate-induced and 5-fluorouracil-induced toxicity [22-24].

Impact on Patients

As reported by patients, mucositis is one of the most significant adverse symptoms of cancer therapy [25,26]. Resources that are needed to manage the acute effects of mucositis and its impact on the patient include, but are not limited to: total parental nutrition, increased use of antifungals and opioid analgesics, increased emergency department visits, and increased hospitalizations [4,27, 28]. The substantial pain and ulceration can lead to a decline in oral health, nutritional status, quality of life, and in severe cases, even death [27,29-31]. The pain associated with mucositis can persist after treatment is complete and its management may require parenteral opioid analgesics [32,33]. Unfortunately, opioid analgesics are not always effective in managing the pain and are associated with aversive side effects such as constipation and a decrease in alertness [9,25,27]. The pain can also interfere with the patient's ability to eat and drink which can lead to weight loss in already frail patients and required initiation of total parenteral nutrition [26].

The ulcerations in mucositis can create a portal of entry for pathogens in a patient that may already be immunocompromised due to myelosuppression [4]. In severe cases, this can lead to life-threatening systemic infections [34,35]. Research has shown that infection occurs in 36% of solid tumor patients receiving myelosuppressive therapy. However, in patients who experience mucositis due to myelosuppressive therapy, the occurrence of infection increases to 73% [15]. Unfortunately, these infections may be hard to prevent and predict because there are no specific criteria for determining risk of infection during myelosuppression [2].

Mucositis can be considered a dose-limiting toxicity. A reduction or delay in treatment may be warranted given complications associated with pain, infection, and inability to eat. As reviewed by Elting et al. [28], mucositis can lead to a dose reduction of chemotherapy in 23%-28% of cycles. These dose reductions are a major source of concern because they can directly diminish cure rates and patient survival [5].

Pathobiology of Mucositis

The emergence of oral mucositis after intensive chemotherapy occurs approximately two weeks after chemotherapy initiation [36], which corresponds to the estimated mitotic rate of oral epithelium of 9 to 16 days [37]. It was previously thought that mucosal toxicity was simply due to the direct toxicity of chemotherapy agents on mucosal cells [38]. However, research has determined that the development of mucositis involves not only the mucosal epithelium, but the submucosa and the extracellular matrix [39]. The pathobiology follows a discrete five phase process that includes: 1. Initiation, 2. Signaling, 3. Amplification, 4. Ulceration, and 5. Healing [6,39] (Table 3). An important implication of this model is that it identifies a variety of potential therapeutic

Phase I – Initiation	Exposure to chemotherapy or radiation causes generation of reactive oxygen species (ROS) and lipid peroxidation. This results in DNA damage and cellular apoptosis
Phase II – Signaling	ROS cause further damage and stimulate the expression of NF- κ B. NF- κ B expression leads to increased production of proinflammatory cytokines (TNF- α , IL-1 β , IL-6)
Phase III – Amplification	Release of proinflammatory cytokines leads to prolonged tissue injury, apoptosis, vascular permeability, and activation of cyclooxygenase-2.
Phase IV – Ulceration	Ulceration occurs, providing a portal for the entry for colonization of microorganisms. Bacteria cause activation of macrophages and further production of proinflammatory cytokines
Phase V – Healing	Signals from submucosa promote epithelial proliferation and differentiation

Table 3: The phases of oral mucositis adapted from [6,39].

targets (e.g. sequesters of free radicals, inhibitors of pro-inflammatory cytokines) that could hinder or reverse the development of mucositis.

Another interesting aspect of the model is that it demonstrates that microorganisms are a coincident condition and not a direct cause of mucositis [6]. In a hamster model of mucositis, the development of lesions preceded increases in bacterial colonization [6]. Even though microorganisms may not directly cause mucositis, it is important to note that the presence of infection can often complicate the diagnosis and management of oral mucositis [40].

Oral Toxicity Caused by Targeted Anticancer Therapy

The use of targeted agents in the treatment of cancer has recently exploded and has had a significant positive impact on patient quality of life and survival rates [1]. Since 2012, 14 agents have been approved by the U.S. Food and Drug Administration [41]. These agents influence or inhibit the signaling of many cellular targets including mTOR, EGFR, vascular endothelial growth factor, hedgehog, human epidermal growth factor receptor 2, and several tyrosine kinases. This explosion of targeted agents represents the products of the extensive research that has occurred in the field of cancer cell biology. However, the presence and function of some of these targets in normal cells is just beginning to be understood. Unfortunately therefore, targeted anticancer therapy can also cause significant toxicity to non-cancer cells.

Mucositis is one of the most commonly reported toxicities of mTOR inhibitors [42,43], and in some studies, it was the dose-limiting toxicity [44]. Oral toxicities with other targeted agents, such as the kinase inhibitors and monoclonal antibodies are less common. Yet studies have shown a significant incidence of all-grade mucositis with bevacizumab, erlotinib, sorafenib, and sunitinib [15,43]. The incidence of oral toxicity associated with targeted agents has been shown to increase as the dose increases [45]. However, unlike with the conventional anticancer agents, subsequent cycles of targeted agent therapy can lead to a decrease in the frequency and severity of oral toxicity [45].

The clinical presentation of targeted agent-induced oral mucositis is quite different from radiation or chemotherapy-induced mucositis. Typically, it has a rapid onset (within 5 days) and is of mild to moderate severity (grade 1-2). The lesions are round and have similar appearance to aphthous stomatitis (canker sores) [12,46]. Another distinguishing feature of targeted therapy-induced oral toxicity is that the lesions are more likely to resolve spontaneously even when treatment is continued [42]. Given these differences, the toxicities seen with targeted agents may be better classified as stomatitis, rather than oral mucositis [12,40,47].

Although the severity of targeted agent-induced oral toxicity is less severe than that caused by conventional chemotherapy, it may still be dose-limiting [12,17,19]. Treatment with targeted agents is often long-term and may continue until the cancer has progressed or unacceptable toxicity occurs. Because many of the targeted agents are taken orally and are self-administered, the negative impact of targeted therapy-induced oral toxicities on patient adherence and treatment outcomes is significant [17,48].

The exact mechanism of how targeted agents produce oral toxicities is likely different than the pathways described for conventional chemotherapy agents. Recent research done in a clinically relevant rat model of tyrosine kinase inhibitor-induced diarrhea has identified that unlike with conventional chemotherapy agents, tyrosine kinase inhibitors do not cause direct damage to mucosal cells [49]. However, apart from that, the targeted agent-induced mechanism is not well-

understood. This may be due in part because targeted agents are often given in conjunction or after conventional anticancer therapies have been given. Therefore, the toxicities of targeted agents can combine with or accentuate the toxicities of conventional chemotherapy and it may be difficult to distinguish toxicities solely caused by the targeted agent.

Future Directions

Recent years have seen an increase in the amount and the momentum surrounding mucositis research in both clinics and in laboratories. Unfortunately, anticancer agents are not currently classified based on their oral mucositis risk [4]. Therefore, strategies for prevention and treatment are still limited and the majority of currently available studies have significant weaknesses [9]. For example, there are few studies that focus on chronic complications and survivorship issues [8]. However, as cancer survivor rates increase, it becomes important to understand the impact of mucositis on the long-term oral health and well-being of the patient [3]. Additionally, given the impact that oral toxicities have on daily functioning, there is a need for research to focus not only on the incidence of oral mucositis and stomatitis, but also on the severity and duration. In order to accomplish this, studies would likely need to increase monitoring between treatment cycles and also incorporate patient-reported symptoms with clinical diagnostic tools [15].

The discovery of the complex pathobiology of mucositis has undeniably created several potential avenues for drug development and research [6]. However, given the complexity of most cancer treatment regimens, it will be challenging to manage the toxicities of simultaneous multiple agents, some of which have an unknown mechanism, without jeopardizing the ultimate goal of destroying cancer cells [50]. For example, it is possible that the desired treatment effect and the undesired toxicity are inseparable and that attenuating toxicity will also lead to reductions in efficacy [51].

Conclusion

As Sonis states, mucositis is toxicity that “largely defies effective intervention” [12,50]. Now that febrile neutropenia and chemotherapy-induced nausea and vomiting are managed with various pharmacologic agents, mucositis has become one of the most troubling dose-limiting toxicities for patients. However, given the tremendous impact that these oral toxicities have on the patient and the healthcare system, urgent studies are needed to develop effective strategies for prevention and treatment.

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