Chemotherapy-induced Oral Mucositis

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Abstract

Oral mucositis is one of the most common side effects cancer patients experience when undergoing chemotherapy. However, it is frequently under-reported and leads to high morbidity and complication rates. Advances in molecular biology have provided greater insight into the pathophysiology of this condition. Although there are no current treatments that completely resolve this painful condition, encouraging research developments indicate that a new, over-the-counter pH-balanced salt solution, reBalance^{Ca}, shows promise.

Keywords

Oral mucosits, oral pain, mouth sores, oral ulcers, chemotherapy-induced side effects, reBalance^{Ca}, xerostomia, oral mucosa, chemotherapy

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Oral mucositis is a common complication of cancer chemotherapy. The incidence of oral mucositis in cancer patients varies widely.[1] In patients receiving high-dose myeloablative therapies, the incidence rate of oral mucositis is nearly 100%.[2] The incidence rate is also high in patients undergoing head and neck cancer treatments,[3] especially if they are receiving concurrent chemoradiotherapy.[4] For these patients, the incidence rate of oral mucositis may be as high as 90%.[4] Patients receiving chemotherapy treatments using certain drugs such as 5-fluorouracil (5-FU)[5] and melphalan[6] have a higher incidence of oral mucositis than those receving other chemotherapy drugs. In general, the incidence rate of oral mucositis in cancer patients undergoing chemotherapy at standard doses is 40–60%.[7]

Oral mucositis in patients undergoing chemotherapy treatments is frequently under-reported.[8] Patients often do not report oral mucositis if the symptoms are mild or if they are not queried about it. Furthermore, the oral mucosa is not always examined by the medical care team. Oral mucositis in its early stages presents with erythema, mild pain, and mild dysphagia that is manageable with over-the-counter medications. Patients often make adjustments in their oral intake by decreasing intake of food and sometimes fluids as well.

When early-stage oral mucositis is identified, there are few effective treatments currently available.[9] Medications such as palifermin[10] and caphasol[11] are indicated for the prevention of oral mucositis in patients undergoing high-dose myeloablative therapies. They are, however, not indicated for the treatment of oral mucositis after chemotherapy has been administered.

In patients undergoing chemotherapy at standard doses, oral mucositis generally presents as grades 1 and 2 rather than grades 3 and 4. Even with these early grade presentations, patients will often not report it to their physicians or to their family members.[12] Patients can rapidly become dehydrated and malnourished and deteriorate to the severity of needing hospitalization.[13]

Mucositis can lead to oral infections including viral, bacterial, and fungal infections.[14,15] The ulceration of oral mucosa is a portal for these infections. If the patient is neutropenic from chemotherapy treatments, the local infection can become systemic.

Neutropenia enhances the degree of oral mucositis. The more serious the neutropenia, the more serious the oral mucositis. Patient quality of life can be affected by oral mucositis, and its consequences can result in treatment delays, hospitalizations, and unintended increases in medical costs.[8,16] Treatment delays in particular can result in poorer outcomes for the patient.

There are no racial[17] or sexual predilections[18] to chemotherapy-induced oral mucositis. Younger patients tend to develop oral mucositis more often than older patients, possibly because of a more rapid turnover of basal cells in the oral mucosa of younger patients.[19]

Recently, several studies[20–22] have shown that the complications caused by oral mucositis in cancer chemotherapy are very significant. These findings have created a broader understanding of oral mucositis and the need to treat it early in its presentation, rather than leaving it as an unmet medical need.

Chemotherapy Drugs Causing Oral Mucositis

Every chemotherapy drug can potentially cause oral mucositis.[23] Drug dose and schedule seem to be key in contributing to the incidence of oral mucositis.[23] Other important factors include the patient's general medical condition (performance status), comorbid conditions, and genetic predisposition (yet to be defined).[24,25] Owing to the variability in the frequency of oral mucositis, the clinician should enquire about the symptoms of oral mucositis and inspect the mucosa frequently. Queries about oral pain and changes in nutritional status can be indicative of oral mucositis in the patient.

The use of biologic agents, especially in combination with chemotherapy, poses additional challenges.[26] The incidence of oral mucositis increases with the addition of biologic agents. There are other complications with biologic agents including allergic reactions, rashes, and other skin reactions.

Pathophysiology

Oral mucositis is a complex interaction of the epithelia and submucosa in response to chemotherapy administration. The interaction of these cells, mediated by reactive oxygen species (ROS),[27] can exacerbate the response, turning an area of erythema into an oral ulcer. Various transcription factors, especially nuclear factor kappa B (NFκB),[28] and a number of proinflammatory cytokines contribute to the amplification of signals, leading to tissue necrosis and ulcer formation.

Sonis[1,19,29,30] has identified five phases in the development of oral mucositis and mucosal restoration. Although these phases are not necessarily sequential, they serve as a useful biologic model for understanding chemotherapy-induced oral mucositis. The five phases of this model are initiation phase, message-generation phase, signaling and amplification phase, ulceration phase, and healing phase.

In the inititiation phase, chemotherapy agents lead to the generation of free radicals such as ROS, and DNA damage ensues. In the next phase, the message generation phase, transcription factors such as NFκB are activated. NFκB is central to the upregulation of a host of proinflammatory cytokines. These cytokines, such as interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) are potent mediators of inflammation. The local site becomes inflamed, edematous, and erythematous.

The next phase is the signaling and amplification phase. In this phase, the proinflammatory factors and cytokines amplify their effect through positive feedback loops. NFκB in particular can activate multiple pathways including the mitogen-activated protein kinase (MAPK) pathway and the sphingomyelinase pathway. This results in increased erythema and progressive cellular and tissue injury. Epithelial atrophy ensues thereafter. This usually occurs at about four to five days after the first dose of chemotherapy, and leads to the next phase, the ulcerative phase.

Oral mucosal ulcerations are very painful. They make swallowing and speech difficult and frequently lead to dehydration and malnutrition. Bacterial and fungal infections can become superimposed as the mucosal epithelium becomes completely disrupted. Reactivation of viral infections such as herpes simplex virus (HSV) is also common. The degree of ulceration is reflected in the dose intensity of the chemotherapy drugs used and the degree of neutropenia. The greater the degree of neutropenia, the more severe the ulceration and the greater the likelihood of infection.

The healing phase is the final phase. New granulation tissue arises from the submucosa and from the edge of the ulcer. As the necrotic, devitalized tissue is sloughed off, fresh granulation tissues arise, and healing is complete.

The involvement of the submucosal tissues in oral mucositis and the inflammatory response amplified by cytokines and various mediators have provided new targets for pharmaceutical therapy to treat and prevent these lesions.

Consequences of Oral Mucositis

The consequences of oral mucositis can have serious implications for the patient. The morbidity of oral mucositis is reflected in the deterioration of quality of life.[31]

Pain

Pain from oral mucositis is the most common and debilitating complication.[32] Pain can be unrelenting and its management difficult. In addition to topical therapies, patients may need systemic therapies in more serious cases. The incidence of pain correlates with the ulcerative phase of oral mucositis. The raw nerve endings in the ulcer crater are exposed to the elements and are extremely painful. The pain of oral mucositis can be so debilitating that other oral activities, such as swallowing, mastication, drinking, and speech, become inhibited. Patients can become dehydrated and malnourished very quickly. In these circumstances, hospitalization with parenteral administration of fluids, analgesics, and total parenteral nutrition (TPN) is warranted.

Local pain therapies such as viscous lidocaine and magic mouthwash have limited benefits.[33,34] Although they provide pain relief, it is very fleeting as the lidocaine wears away after only a few minutes. Patients have difficulty sleeping because of the long duration without analgesia.

Gelclair[35] is a topical treatment that adheres to the mucosal surfaces of the mouth. It forms a protective coating that shields nerve endings and provides a measure of pain relief. It too provides temporary pain relief. Gastrointestinal (GI) drugs such as sucralfate[34] also form a viscous adhesive coating on the oral mucosa and GI lining. Its effectiveness in upper GI tract ulceration such as stomach ulcers is established, but its benefit in oral mucositis is limited.

Infections

Infection in the oral cavity is another important complication of oral mucositis. The ulcers of oral mucositis become portals for colonization by infectious agents. Candidal infections can be superimposed on oral mucositis, requiring treatment of both conditions. Antifungal agents such

as nystatin (swish and swallow)[36] and clotrimazole (troche) are effective local antifungal agents. For systemic antifungal therapy, fluconazole[37] is beneficial. Antiseptic mouth washes such as chlorohexadine[38,39] can reduce the bacterial load in the oral cavity. Antiviral therapies such as aciclovir, valaciclovir, and famciclovir are effective treatments for reactivation of HSV[40] in the oral cavity. Treatment of infections, however, does not clear oral mucositis.

Malnutrition

Malnutrition in patients with oral mucositis is a common presentation. The degree of oral mucositis is often correlated with the severity of malnutrition. In the more severe cases of oral mucositis, TPN may be necessary. Dysphagia (pain with swallowing) and dehydration are frequently present with malnutrition. Nutritional supplements can be helpful in those instances where the patient may not tolerate solids but can still tolerate liquids.

The grading of oral mucositis lesions is based on physical findings such as erythema and presence of ulcers as well as the nutritional abilities of the patient. Whether the patient can tolerate solid foods or liquids only, or neither, contributes to the grade of mucositis.

The World Health Organization (WHO) grading scale for oral mucositis is closely tied to the nutritional abilities of the patient. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale closely resembles the WHO scale by incorporating nutritional criteria as well. Two other scales commonly used to grade oral mucositis are the Radiation Therapy Oncology Group (RTOG) scale and the Oral Mucositis Assessment Scale (OMAS). These scales do not use nutritional criteria for grading oral mucositis. *Table 1* shows the different grading scales for oral mucositis. The ability of the patient to tolerate oral intake of liquids and solids remains crucial to the morbidity of oral mucositis. Strict attention to the nutritional abilities of the patient is critical to the patient's outcome.

Treatment Delays

Cancer patients on chemotherapy can have treatment delays and treatment modifications (dose reduction) because of oral mucositis. Patients who develop oral mucositis with one cycle of chemotherapy will likely develop it again with subsequent cycles of chemotherapy. The patient and clinicians are then faced with difficult decisions about further chemotherapy treatment modifications or discontinuation. Some patients may choose to forgo chemotherapy treatments altogether rather than suffer from grade 3 or 4 mucositis. Chemotherapy dose reductions can decrease the benefit of treatment. Until better treatments are available for the treatment of oral mucositis, patients and clinicians may have to face difficult treatment choices.

Quality of Life

Oral mucositis has a major impact on a cancer patient's quality of life.[31] Being able to manage oral mucositis and all the consequences of its presentation, especially pain, infections, and malnutrition, is a challenge to clinicians.

Treatment of Oral Mucositis

Patients with oral mucositis can become extremely debilitated, and their quality of life greatly diminished. Unfortunately, there are only a few established treatments for oral mucositis, and their effectiveness is variable. Some of the most common treatments are detailed below.

Table 1: Different Grading Scales for Oral Mucositis

Scale	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO	None	Erythema, regular meals	Ulcers, some solid foods	Ulcers, liquid diet only	Ulcers, no food or water
RTOG	None	Erythema	Confluent patches <1.5cm	Confluent patches >1.5cm	Necrosis, deep ulcers
NCI-CTC	None	Erythema, painless ulcers	Painful ulcers, can eat/swallow	Painful ulcers, needs IVF	Severe ulcers, TPN required
OMAS	Normal	Not severe <1cm ulcer	Severe 1–3cm ulcer	Severe >3 cm ulcer	NA

IVF = intravenous fluids; NCI-CTC = National Cancer Institute Common Toxicity Criteria; OMAS = Oral Mucositis Assessment Scale; RTOG = Radiation Therapy Oncology Group; TPN = total parenteral nurition; WHO = World Health Organization.

Salt Rinses

Salt rinses have been advocated as being potentially helpful in treating oral ulcers and oral pain and improving dental health. Homemade salt solutions incorporating table salt and sometimes baking soda have been recommended by dentists to improve dental hygiene. Their benefit in treating oral mucositis, however, is anecdotal.[33]

Oral Debridement

Oral debridement can clear the oral mucosa of debris and devitalized tissues. With a soft toothbrush and/or sponge applicator, the oral mucosa, teeth, gums, and tongue can be brushed to debride overgrowth, clear dried saliva, and reduce pseudomembranes. Frequent rinsing with water will help wash away the debris and may improve oral health.

Prevention and Growth Factors

New understanding of the biologic process of oral mucositis has highlighted the potential of growth factors in preventing oral mucositis. Several growth factors, including granulocyte colony-stimulating factor (G-CSF),[41] granulocyte–macrophage colony-stimulating factor (GM-CSF),[42–44] transforming growth factor-beta (TGF-β3),[45] and palifermin (recombinant human keratinocyte growth factor) are undergoing clinical studies in the prevention of oral mucositis.

Of these, palifermin[46,47] has some potential in preventing the development of oral mucositis. It mediates epithelial cell growth and repair. It also decreases TNF-α, which is a proinflammatory mediator, and in the process facilitates mucosal healing. The action of the drug appears to be bi-modal, with a growth-enhancing differentiation and a cytoprotective effect throughout the GI tract.

In a double-blind, placebo-controlled study of palifermin,[10] 212 patients with hematologic cancers were treated for three days before and three days after transplant. It was reported that there was a decrease in grade 3 and 4 oral mucositis, with 63% of palifermin-treated patients developing oral mucositis versus 98% of those in the placebo group ($p<0.01$). Additionally, there was a decrease in patient-reported

soreness of mouth and throat, narcotic analgesic use, and use of TPN. The benefit of palifermin in the prevention of oral mucositis in the transplant setting is being duplicated in other high-dose chemoradiotherapy settings, including treatments for head and neck cancers.[48]

Cryotherapy

Cryotherapy (ice chips) is an inexpensive and readily available treatment. Studies evaluating cryotherapy noted benefits in patients who chewed on ice for 30 minutes before each 5-FU chemotherapy infusion.[26,39] The incidence of oral mucositis and the degree of oral mucositis (incidence of grade 3 and 4) were mildly diminished with cryotherapy. Cryotherapy does not benefit all patients receiving chemotherapy drug treatments.[49] For example, patients treated with methotrexate had no preventive benefits from cryotherapy.[50,51] Clinical trials with cryotherapy are difficult to design because it is impossible to have a blinded randomized trial with a cryotherapy arm.

A New Balanced Salt Solution—reBalance^{Ca}

A new balanced salt solution, reBalance^{Ca} (Vaxco Pharmaceuticals, Kansas City, KS), appears to be promising. reBalance^{Ca} is a physiologically balanced salt solution formulated for the healing of oral lesions. The rinse provides a soothing physiological environment that promotes rapid healing of oral tissues. reBalance^{Ca} is indicated for cancer patients undergoing chemotherapy treatments who develop oral mucositis. It is also indicated for cancer patients undergoing radiation treatments, especially to the head and neck areas, who develop oral mucositis. reBalance^{Ca} may also help with xerostomia (dry mouth).

The formulation is based on solutions used in cell culture work. Balanced salt solutions that are buffered and pH-titrated are necessary for the propagation of cell lines in the laboratory. Using this same principle, reBalance^{Ca} was developed with some modifications. The solution is intended to help the oral mucosa heal ulcers that have developed as a consequence of chemotherapy administration.

One study (Raj Sadasivan, MD, PhD, unpublished data) involving 48 patients who were undergoing cancer treatments showed excellent relief of symptoms, especially pain: 97% of patients reported significant relief of pain within 24 hours of using reBalance^{Ca}, and 94% of patients reported total resolution of pain symptoms within three days (average 1.9 days). Relief of symptoms resulted in improved swallowing, eating, and drinking, improved appetite, a decrease in the use of oral pain medications, and improved hydration. Relief of symptoms lasted for the duration of use of reBalance^{Ca}. Careful inspection of the oral mucosa by the medical care team and detailed patient diaries confirm the effectiveness of this product compared with historical data, where the lesions of oral mucositis took more than four days to heal with salt rinses.

reBalance^{Ca} mouth rinse is an over-the-counter balanced salt solution that is buffered to simulate physiologic pH. It contains a wetting agent, glycerin, that permits the salt solution to adhere to mucus membranes, thereby facilitating the healing of ulcers. It contains no alcohol or hydrogen peroxide. It is non-acidic and non-corrosive. It is simple to use, with the patient rinsing his or her mouth with one to two capfuls three to six times daily. reBalance^{Ca} is non-toxic, has no known adverse side effects, and can be used in special populations, including pregnant women, nursing mothers, children over the age of six, patients with diabetes, patients with hepatic or renal impairment, and the geriatric population.

The promise of this mouth rinse is in its effectiveness. Additional studies corroborating the current findings and new clinical trials in radiation therapy and in the preventive setting are under way.

Conclusion

Oral mucositis is a very serious complication of cancer chemotherapy. Pain, malnutrition, dehydration, and risk of infections all contribute to the morbidity of oral mucositis. These serious complications can lead to treatment delays or treatment termination, hospitalization, and increased medical costs. One agent that has recently undergone phase II testing, reBalance^{Ca}, shows considerable promise as a very high percentage of patients (97%) experienced significant relief of pain and improvement of symptoms within 24 hours of use. It is hopeful that reBalance^{Ca} will prove effective in the preventive setting. Improved treatments for oral mucositis will have a positive impact on patient quality of life. ■

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