Potential Benefits of Oral Cryotherapy for Chemotherapy-Induced Mucositis

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Mucositis is a common side effect of cancer therapies that causes painful, erythematous lesions to develop in the gastrointestinal tract. These lesions can lead to malnutrition, increased risk for serious infection, prolonged hospital stays, and reduced quality of life. Oral cryotherapy, or the use of ice chips to cool the mucous membranes during bolus chemotherapy infusions (e.g., 5-fluorouracil [Adrucil®] and melphalan [Alkeran®]), is the most readily accessible and cost-effective intervention available. Although many factors may contribute to the development of mucositis during cancer treatment, studies have found a reduction in the incidence and the severity of mucositis with the use of oral cryotherapy.

At a Glance
• Chemotherapy-induced mucositis often occurs following most standard doses of chemotherapy.
• Current mucositis prevention techniques vary in cost, effectiveness, and accessibility.
• Oral cryotherapy is a low-cost, low-risk intervention that has been shown to reduce the severity of chemotherapy-induced mucositis.

Oral mucositis is a common side effect of cancer treatments, such as radiation and chemotherapy, with a high degree of symptom burden that decreases quality of life, prolongs hospital stay, and may require dose limitation for future therapies (Lalla, Saunders, & Peterson, 2014). Chemotherapy-induced mucositis occurs in 40% of patients who receive standard dose therapies and in almost all patients who receive high doses in preparation for hematopoietic stem cell transplantation (HSCT) (Stringer, 2013). Most patients undergoing HSCT cite oral mucositis as the most debilitating complication (Lalla, Saunders, & Peterson, 2014). The presence of mucositis often has negative effects on the patient’s tolerance of cancer treatments, and complications arising from mucositis can have a significant impact on survival. Because of this, many randomized, controlled trials have been devoted to finding the most effective mechanisms of mucositis prevention.

Mucositis Development and Assessment Tools

Mucositis presents in varying degrees of severity, often progressing from mild to severe. Al-Dasooqi et al. (2013) describes the manifestations of oral mucositis as part of a continuum ranging from mild erythematous atrophic lesions to ulcerative lesions that extend to the mucosa. The grading of mucositis is determined by a combination of visual inspection of the oral mucosa, pain assessment, and evaluation of functional status in terms of nutritional intake. Two grading scales, one from the National Cancer Institute (NCI) and one from the World Health Organization (WHO), are widely used in oncology practice (see Table 1). The NCI scale is more favorable because it includes a functional and pain assessment with each grade of mucositis, which prompts oncology nurses to consider the need for nutritional or pain-relieving interventions.

Understanding the pathophysiology of mucositis development is essential for oncology nurses to best determine how to incorporate techniques of oral mucositis treatment and prevention. Georgiou, Patapatiou, Domoxoudis, Pistevou-Gompaki, and Papanikolaou (2012) best summarized the evolution of mucositis by describing the five steps of mucositis development, which consist of initial injury to cells by chemotherapy via direct DNA damage or reactive oxygen species, a series of enzyme and transcription factor activation, the upregulation of inflammatory cytokines, inflammation and tissue damage, and the eventual healing of the extracellular matrix. This process can last 3–12 days if induced by chemotherapy and much longer if mucositis is a result of radiation therapy (Georgiou et al., 2012). A more in-depth understanding of this pathogenesis aids in the prediction of toxicity risk with cancer therapies and helps nurses to implement...
more personalized interventions to reduce negative effects of mucositis, such as pain, infection, and malnutrition.

**Morbidity and Economic Cost of Mucositis**

The morbidity and economic cost of severe oral mucositis have prompted the development of prevention strategies. Severe mucositis can cause complications that extend hospital length of stay and may require supportive therapies, such as IV hydration, total parenteral nutrition, and patient-controlled analgesia, until healing can occur over time (Murphy, 2007). The increased cost of the management of severe mucositis stems from the implementation of these supportive therapies and the prolongation of hospital stays that they necessitate. One study of patients undergoing HSCT found that those with severe ulcerative mucositis stayed an average of 4.2 additional inpatient days compared to those with lower grades of mucositis; the study also cited reasons for delay in discharge to be related to dietary limitations, pain management, and presence of fever (Vera-Llonch, Oster, Ford, Lu, & Sonis, 2007). The increased presence of fever in severe ulcerative mucositis correlates with the increased risk of infection secondary to the compromised mucous membranes. The study by Vera-Llonch et al. (2007) also found an increased incidence of infection and a 3.9-fold increase in 100-day mortality risk in patients with higher grades of oral mucositis. Local mucosal infections, which can potentially lead to systemic sepsis, are a significant mortality risk in ulcerative mucositis, particularly in those receiving immunosuppressive therapies, such as HSCT (Lalla, Saunders, & Peterson, 2014). Oncology nurses should be aware of the economic burden and morbidity of severe ulcerative mucositis, and all efforts toward its prevention should be implemented.

**Mucositis Prevention and Oral Cryotherapy**

Some of the most studied prevention strategies include the administration of keratinocyte growth factor-1 (palifermin); the use of low-level laser therapy, benzydamine mouthwash, and chlorhexidine mouthwash; and oral cryotherapy (Eilers, Harris, Henry, & Johnson, 2014). Oral cryotherapy, or the use of ice chips to cool the mucous membranes prior to chemotherapy infusion, is by far the most accessible and cost effective of these prevention strategies. Although many organizations support the use of oral cryotherapy, the Multinational Association of Supportive Care in Cancer partnered in 2014 with the International Society of Oral Oncology to update guidelines on mucositis management (Lalla, Bowen, et al., 2014). The authors of the guidelines support the use of oral cryotherapy for the prevention of mucositis in patients receiving bolus therapies, such as melphalan (Alkeran®), prior to stem cell transplantation and bolus 5-fluorouracil (Adrucil®) for treatment of gastrointestinal cancers.

Oral cryotherapy is a technique that has been studied extensively since the 1990s, with the intention of preventing or reducing the severity of mucositis during chemotherapy infusion (Petersen et al., 2013). The cooling of the oral mucous membranes with ice chips causes hypothermic vasoconstriction of blood vessels in the buccal membrane, which limits the exposure of cytotoxins to the mucosa (Kadakia, Rozell, Butala, & Loprinzi, 2014). For best results, the patient should begin to hold ice in his or her mouth at least 5–15 minutes prior to the start of the infusion. The patient should then continuously swish the ice in his or her mouth for the duration of the infusion while frequently replenishing the ice chips (Mahood et al., 1991). Oral cryotherapy has been studied in bolus chemotherapy infusions, or infusions lasting an hour or less. This is a generally well-tolerated intervention, with the most common side effects being headache, cold sensitivity, and mouth numbness (Mahood et al., 1991).

**Oral Cryotherapy in the Literature**

Although many factors throughout the course of treatment affect the development of mucositis, including hydration status, oral health prior to treatment, and patient adherence to a consistent oral hygiene regimen, many studies have been able to consistently attribute oral cryotherapy to the prevention, reduction in severity, and shorter duration of oral mucositis through the use of randomized, controlled trials. The first of these trials (Mahood et al., 1991) found that the use of oral cryotherapy during infusion of bolus 5-fluorouracil reduced the incidence of mucositis by about 50%. Several confirmatory analyses followed, and similar results were produced (Kadakia et al., 2014).

Oral cryotherapy has been shown to reduce the duration and severity of mucositis with bolus 5-fluorouracil infusions. Two randomized, controlled trials by Papadou, Naxakis, Rigas, and Kalofonos (2007) and Sorenson,

**TABLE 1. Oral Mucositis Grading Scales**

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<tr>
<th>Grade</th>
<th>Definition</th>
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<tr>
<td>1</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
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<tr>
<td>2</td>
<td>Moderate pain not interfering with oral intake; modified diet indicated</td>
</tr>
<tr>
<td>3</td>
<td>Severe pain interfering with oral intake</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
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<tr>
<td>5</td>
<td>Death</td>
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Skovsgaard, Bork, Damstrup, and Ingeberg (2008) studied the incidence of mucositis in 5-fluorouracil-based regimens, with both showing similar benefits to the use of oral cryotherapy. The study by Papadeas et al. (2007) showed a reduction in the incidence and mean grade of mucositis with the use of oral cryotherapy compared to a control group with no intervention. After the first dose of 5-fluorouracil, only 5% of patients in the oral cryotherapy group developed grade 2 or higher mucositis, whereas 15% developed grade 2 mucositis and 5% developed grade 3 mucositis in the control group. The study by Sorenson et al. (2008) randomized patients receiving bolus 5-fluorouracil therapy to three different mucositis prevention strategies: (a) oral cryotherapy prior to infusion, (b) three times daily saline mouth rinses on days 1–21, and (c) three times daily chlorhexidine mouth rinses on days 1–21. This study found a significant reduction in the duration of mucositis in the oral cryotherapy group, with only 15% of patients experiencing mucositis longer than seven days, compared to 25% and 27% in the chlorhexidine and saline groups, respectively (Sorenson et al., 2008). In addition, a reduction in the incidence of severe mucositis, grade 3 or higher, was noted in the oral cryotherapy group, with only 10% of patients having grade 3 mucositis compared to 11% in the chlorhexidine group and 32% in the saline group (Sorenson at al., 2008). Cryotherapy has also been studied in the hematologic malignancy population in conjunction with autologous stem cell transplantation (ASCT) conditioning regimens. Two randomized, controlled trials by Toro et al. (2014) and Salvador, Azusano, Wang, and Howell (2012) studied the effect of cryotherapy in patients receiving high-dose melphalan infusion chemotherapy as a conditioning regimen prior to ASCT. Both studies reported a decrease in the incidence of severe mucositis and were in favor of its implementation into oncology clinical practice as a mucositis prevention strategy for patients undergoing ASCT. Toro et al. (2014) found that 90% of patients in the cryotherapy group did not experience any grade of mucositis compared to only 34% in the saline group. Salvador et al. (2012) found a statistically significant difference between mean mucositis scores based on the WHO grading scale on day 9 following high-dose melphalan infusion, with a mean mucositis score of 0.43 in the oral cryotherapy group compared to a mean score of 1.14 in the conventional therapy group whose members practiced oral care following infusion. A meta-analysis by Wang et al. (2015) summarized that the results of these studies were mostly in favor of oral cryotherapy but should be cautiously interpreted because of the risk of bias and the use of a relatively small sample size.

Conclusion

Oral cryotherapy has been studied extensively since 1991, with generally positive results in the prevention or reduction of severe mucositis in patients receiving bolus chemotherapies, particularly 5-fluorouracil and high-dose melphalan. Because oral cryotherapy is highly accessible and cost effective with limited side effects, its incorporation into oncology clinical practice has few barriers. However, its effectiveness is limited to the duration of infusions, the half-life of the particular agent, and the ability of the patient to tolerate buccal cooling for the intended period of time. Evaluation of cryotherapy effectiveness and its tolerability in infusions of longer duration have yet to be studied; this is likely because of the infeasibility of consistent mucosal cooling for extended periods of time. Randomized, controlled trials studying cryotherapy are limited by the inability to use a double-blinded design, increasing the risk of bias with daily mucositis grading. Determining the true effectiveness of oral cryotherapy is difficult because many factors affect the development of mucositis. Despite these compounding factors limiting data interpretation, the potential benefit of incorporating oral cryotherapy into preventive care cannot be overlooked.

References


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