

## Reducing the Incidence and Severity of Oral Mucositis—Can It Be Done?

a report by

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Advances in radiotherapy and chemotherapy have had a significant beneficial impact on treating cancer. However, despite the increasing sophistication of cancer therapies, oral complications remain a major source of illness for cancer patients. The National Cancer Institute estimates that the frequency of oral complications during radiation therapy to fields involving the oral cavity is 100%, and 40% for primary chemotherapy.<sup>1</sup> Oral mucositis (OM) is one of the most common oral complications related to cancer therapies. OM is thought to affect 5–15% of cancer patients, although the frequency varies depending on the specific cancer treatment.<sup>2</sup> In patients receiving conventional chemotherapy, approximately 40% will experience OM,<sup>3</sup> and rates as high as 70% have been reported for mucotoxic chemotherapy regimens containing 5-fluorouracil (5-FU).<sup>4</sup> In hematopoietic stem cell transplantation (HSCT) recipients, rates of 75–85% have been estimated.<sup>2</sup> OM is a particular concern in patients undergoing radiation therapy for head and neck cancer and can affect nearly all patients undergoing this treatment modality.<sup>5</sup> OM usually manifests within seven to 14 days after the initiation of therapy<sup>6</sup> and can have a significant impact on resource use, costs, and quality of life for patients.<sup>7</sup> The presence of OM can also result in delays or interruptions in treatment, and also dose reductions, all of which have an impact on cure rates.

### Pathophysiology of Oral Mucositis

In recent years the integration of molecular and cellular studies, animal studies, and clinical human trials has helped to improve our understanding of the pathogenesis of OM, and new evidence continues to improve our knowledge of the events surrounding OM. The development of OM is the result of a series of complex biological events that occur throughout different cellular and tissue compartments of oral mucosa. A five-phase model has been proposed to explain the observed clinical phenomena of OM,<sup>5,8</sup> including:

- phase I—an initiation phase that occurs through DNA damage to the basal epithelium cells by radiation and/or chemotherapy, causing a significant

increase in the level of reactive oxygen species (ROS), which in turn triggers the cell signaling process toward ulceration;

- phase II—a message-generation period where DNA strands break, resulting in the initiation of several transduction pathways. This phase results in a positive feedback loop, which leads to phase III;
- phase III—the signaling and amplification stage. Eventually, amplification of transduction pathways leads to phase IV;
- phase IV—the breakdown of the epithelial mucosa causes ulceration; and
- phase V—the healing phase, in which cells in the extracellular matrix signal to epithelial cells to begin dividing, starting the process of mucosal renewal.

The development of OM is dependent on both treatment-related and patient-related factors. Several signaling mechanisms and pro-inflammatory cytokines have been proposed as mediators in the development of OM, including tumor necrosis factor (TNF), interleukin-6 (IL-6), IL-1 $\beta$ , nuclear factor kappa-B (NF $\kappa$ B), and ceramide synthase.<sup>5,8–10</sup>

### Risk Factors for Oral Mucositis

The risk for developing OM varies between patients receiving radiation therapy and those receiving chemotherapy. Irradiated tissue remains at a high risk for developing OM throughout life; however, the risk for OM in those receiving chemotherapy reduces over time after the treatment protocol. Normal repair mechanisms are highly compromised in radiotherapy as a result of permanent cellular eradication.<sup>11,12</sup> The prevalence of severe OM in patients receiving a combination of chemotherapy and radiotherapy is 100%, compared with 60% in those receiving chemotherapy alone.<sup>13,14</sup> Patient-specific risk factors have also been identified for the development of OM. Prior dental problems including gingivitis, periodontal disease, dental plaques, dental caries, and improperly fitting prostheses have been demonstrated to increase the risk for OM.<sup>15</sup> To reduce the risk of mucositis, an effective oral hygiene program is recommended that includes consistent rinsing of the oral cavity to decrease the level of oral oropharyngeal flora.<sup>16,17</sup> Younger cancer patients have a higher mucosal turnover rate, increasing their susceptibility to mucositis, and it has been estimated that children who have a high rate of proliferating basal cells are three times more likely to experience mucositis than elderly adults.<sup>9,18</sup>

### Clinical Implications of Oral Mucositis

OM can have significant clinical implications for cancer patients. OM is associated with pain and increased risk for infection, and can lead to impaired nutritional status and inadequate hydration. Furthermore, OM may have a detrimental impact on the outcome of cancer treatment due to dose-limiting toxicity, which may require a treatment interruption in some patients. Data from the Caphosol Relives Oral Mucositis (CARE OM) support program, which



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included 427 treated cancer patients who had or who had previously suffered from OM, showed that 8% of respondents had missed a dose of cancer treatment because of OM; importantly, of those patients 11 (31%) did not tell their physician about the missed dosage.<sup>19</sup> Patients were surveyed for attitude, usage, and awareness to obtain a better understanding of the disease and the experiences of patients.

### Standard-dose Chemotherapy

Although the degree and duration of OM are dependent on the dose and schedule of the chemotherapy regimen and the specific regimen itself, the clinical course of OM in patients undergoing standard-dose chemotherapy is variable, although OM generally begins four to five days after treatment and resolves within three weeks. The chemotherapy agents cyclophosphamide, methotrexate, 5-FU, and cisplatin are associated with the highest risk for chemotherapy-related OM.<sup>20</sup> Furthermore, in some cases the presence of OM may require future doses of chemotherapy to be reduced and hence could compromise the overall effect of treatment.<sup>21</sup> Patients receiving standard-dose chemotherapy who experience OM also have weight loss in 61% of cycles, with 11% of patients with grade 3 or 4 OM requiring a liquid diet and 10% requiring total parenteral nutrition.<sup>7</sup> Furthermore, in patients undergoing standard-dose chemotherapy who experience grade 3–4 OM, 70% require feeding tubes.<sup>22</sup> Elting and colleagues reported that the incremental costs of hospitalization associated with OM could exceed \$3,500 per cycle of standard-dose chemotherapy due to the greater need for fluid replacement, total parenteral nutrition, and antifungal and antiviral treatments.<sup>7</sup> The same study also found that severe OM resulted in dose reductions and/or delays in therapy.

### Hematopoietic Stem Cell Transplantation

In HSCT patients, OM develops approximately seven days after patients commence therapy.<sup>23</sup> The symptoms of OM worsen over the next seven days before stabilizing at the maximum level of severity. The development of OM in HSCT patients has been associated with a rise in systemic infections due to the disruption of the mucosa.<sup>24</sup> Indeed, in patients undergoing autologous transplant, those with OM had a three-fold increase in the rate of bacteremia.<sup>25</sup> It is estimated that 87% of adult and 90% of pediatric HSCT patients will require total parenteral nutrition or feeding tubes.<sup>22,26</sup> HSCT patients who develop OM have both an increased average length of hospital stay and other complications associated with HSCT.<sup>26</sup> Furthermore, HSCT patients suffering with OM incur additional costs of \$43,000, along with increased mortality and more days in hospital.<sup>26</sup>

### Radiation and Chemoradiation Therapy

In almost all cases radiation therapy and chemoradiotherapy for head and neck cancer result in OM.<sup>5</sup> The rate, severity, and duration of OM can vary depending on the cumulative dose, fractionation, involved field, the volume of irradiated mucosa, and other predisposing factors, such as smoking.<sup>27–30</sup> OM associated with radiation therapy and chemoradiotherapy is usually observed within three weeks of initiating radiation treatment. Symptoms generally worsen before peaking at five to seven weeks.<sup>31,32</sup> The general consensus is that OM will resolve over four to eight weeks, although a recent study suggests that radiation-induced OM may last longer than had been previously documented.<sup>33</sup>

The pain and swelling associated with OM can lead to long-term alterations in swallowing function, leading to weight loss and aspiration and nutritional depletion; however, in patients with head and neck cancer

there may be several contributing factors, including OM.<sup>34</sup> One study examined swallowing function in head and neck cancer patients who had undergone a dose of chemotherapy in combination with radiotherapy and found that prior to treatment all patients had normal to mild dysphasia, although three months after treatment a significant percentage of patients suffered from moderate or severe swallowing dysfunction.<sup>35</sup> Interestingly, 12 months after chemotherapy treatment swallowing function returned to baseline for the majority of patients. Results from the study indicated that the risk of swallowing dysfunction is dependent on the treatment program used. The Longitudinal Oncology Registry of Head and Neck Carcinoma showed that 27% of patients had feeding tubes placed before the initiation of therapy and that this number increased as patients developed OM-related toxicities.<sup>36</sup> OM has also been associated with more frequent use of long-term tube feeding after radiotherapy treatment for head and neck cancer.<sup>37,38</sup>

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Unplanned treatment breaks and reductions in treatment dose intensity can decrease the efficacy of radiation therapy and chemoradiation therapy, allow tumor re-growth, or result in lower response rates, poorer quality of life, and decreased survival.<sup>7</sup> In 450 patients receiving radiation therapy for head and neck cancer, OM was found to lead to more breaks in radiation treatment and hospital administrations.<sup>39</sup> In the study, 83% patients received standard radiation therapy and one-third were treated with concomitant chemotherapy. OM occurred in 83% of patients, and these patients had a greater frequency of unplanned radiation treatment breaks and hospitalizations. Intensity-modulated radiation therapy (IMRT) has been shown to produce a non-significant trend toward a decreased incidence of grade 3–4 OM compared with standard radiation therapy.<sup>40</sup> OM developed in 97–100% of cases. The study also found no difference in dose delays or reductions between radiation types or use or non-use of chemotherapy. A systematic literature review found that in five studies 11% of patients required an unplanned interruption or modification in their radiation therapy regimen due to mucositis; the frequency rose to 19% for those receiving chemoradiation therapy.<sup>30</sup>

As with OM related to chemotherapy and HSCT, radiation-induced OM is associated with increased costs. A retrospective study<sup>41</sup> conducted in 204 patients with squamous cell carcinoma of the head and neck treated with radiation (conventional or intensity-modulated) alone or combined with chemotherapy found a direct relationship between increased cost and grade of OM. OM was associated with an incremental cost of \$1,700–6,000, depending on the grade of OM.

### Strategies to Prevent Oral Mucositis

Historically, the management of OM has centered around the use of palliative measures. However, recent focus has been on the prevention or

reduction of the risk for OM. Indeed, clinical practice guidelines developed by the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) provide recommendations for both the prevention and treatment of mucositis.<sup>2</sup> The recently updated guidelines include recommendations for the use of oral care protocols that incorporate patient education aimed at reducing the severity of therapy-related OM.<sup>20</sup> The guidelines also stressed the need for improved educational programs for health professionals, patients, and care-givers. The updated guidelines also introduced recommendations against specific practices: sucralfate and antimicrobial lozenges are not recommended for the prevention of radiation-induced OM because of a lack of evidence confirming their benefit, and use of granulocyte-macrophage colony-stimulating factor mouthwashes in transplantation patients is not recommended due to the lack of supporting data.

### Cryotherapy

Cryotherapy is an alternative method for preventing the rapid infusion of chemotherapy agents into tissues and has been proposed as a method to reduce the burden of OM in high-risk cancer patients. Sixty patients were randomized to receive cryotherapy through rounded ice cubes five minutes before chemotherapy: 90% of the control group suffered from OM compared with 36.7% in the study group.<sup>42</sup> The current MASCC/ISOO guidelines recommend cryotherapy for the prevention of OM associated with bolus 5-FU, edatrexate, and high-dose melphalan leucovorin.<sup>20</sup>

### Kepivance

Kepivance® (palifermin, Amgen) is a recombinant human keratinocyte growth factor (KGF) that promotes epithelial cell proliferation to reduce the incidence of severe mucositis. It is indicated to decrease the incidence and duration of severe OM in patients with hematological malignancies receiving myelotoxic therapy requiring HSCT. Kepivance is given intravenously for three days prior to chemotherapy and administered three days after treatment. A phase III trial

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demonstrated that palifermin decreased the incidence of OM from 93% in controls to 63% in the study group in patients with hematological malignancies.<sup>43</sup> Patients treated with palifermin reported significant improvements in overall wellbeing and decreases in throat soreness and swallowing difficulties. Adverse effects in the palifermin-treated group were slightly increased compared with those in the control group in the phase III trial, and were noted as rash, pruritus, erythema, cough, and edema.<sup>43</sup> However, all of these conditions were mild and did not result in the discontinuation of palifermin. Concerns have been raised that palifermin may negatively affect chemotherapy and radiotherapy since many non-hematological malignancies express the KGF receptors. In one study, palifermin

was shown to stimulate proliferation of in human endometrial carcinoma cells and additionally has been shown to enhance the growth of human epithelial tumor cell lines *in vitro*.<sup>44</sup> Furthermore, in nude mice xenograph models palifermin increased the level of tumor cell line growth in a human carcinoma.<sup>45</sup> Reports to date have pointed toward a benefit of palifermin for use in the HSCT setting; however, there is a lack of evidence for the benefit of palifermin in non-hematological malignancies. Palifermin is currently being evaluated for use in patients with head and neck cancer, non-small-cell lung cancer, and sarcoma; data from these trials will determine the efficacy of palifermin in reducing OM incidence. The latest MASCC/ISOO guidelines include recommendations for the use of palifermin for OM associated with HSCT, but the high cost of the agent means that its use for prevention cannot be justified when the risk for severe OM is low.<sup>20</sup>

### Caphosol

Caphosol (Cytogen Corp) is an electrolyte solution used as a mouthrinse. It is currently indicated as an adjunct to standard oral care in treating OM that may be caused by radiation or high-dose chemotherapy. Caphosol is also indicated for hyposalivation or xerostomia regardless of the cause. Caphosol is proposed to work through lubricating the mucosa, which helps to maintain the integrity of the oral mucosa to prevent pain from OM. Caphosol's mechanism of action is not fully understood, but it differs from other mouthwashes in that it contains a high concentration of calcium and phosphate ions, which are hypothesized to diffuse into intracellular spaces in the epithelium and penetrate the mucosal lesion that occurs in OM.<sup>46</sup> Two studies have demonstrated that Caphosol is well-tolerated and reduces the incidence of OM in patients receiving HSCT and head and neck radiotherapy.<sup>47,48</sup> A more recent placebo-controlled trial has confirmed these positive results, showing that the severity of OM was significantly lower in the group treated with Caphosol compared with the control group.<sup>49</sup> However, this study was conducted in a single center with patients on different treatment regimens, although the results are similar to those of the previous retrospective studies. Currently, an open-label, multicenter trial (COMFORT) is being conducted that includes patients who are waiting to receive radiotherapy and/or chemotherapy with the risk of developing OM. In our institution the normal standard of care to prevent the risk of OM includes the use of Caphosol, particularly in patients receiving radiation therapy that involves the oral mucosa or the oropharynx. All patients are started on Caphosol from day one of their treatment and continue with Caphosol all the way through their treatment, as well as post-treatment. Thus far, up to 25 patients have been treated with Caphosol. Anecdotal evidence suggests a high rate of patient satisfaction and compliance with Caphosol and a trend toward a reduction in the use of feeding tubes and narcotics in head and neck cancer patients. In terms of safety, no adverse reactions related to Caphosol have been reported in our patients.

### Conclusion

OM remains a frustrating challenge for healthcare providers and a debilitating obstacle for patients. Although palliative therapy is the main option and is still an important goal, greater understanding of the pathogenesis of OM has helped to focus attention on the possibility of preventative strategies. Cryotherapy and palifermin are both means to reduce the risk of OM development for high-risk patients. However, neither therapy is currently accepted universally. Caphosol, an electrolyte mouthrinse containing high concentrations of calcium and phosphate, has been used successfully to eliminate pain in OM sufferers and has been demonstrated to decrease the severity of inflammation. Several other new approaches,

including the free-radical scavenger amifostine, antioxidants, and an L-glutamine oral suspension, are being evaluated for minimizing OM. However, to gain universal acceptance, especially in head and neck cancer treatment, a product must show consistent results and be easily

administered. In the radiation therapy setting, prospective randomized trials comparing the benefits of specific treatments for OM will be insightful, as will prospective trials looking at the association between the dose of radiation and the incidence of OM. ■

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