

# Cancer Therapy-Related Oral Mucositis

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*Abstract:* Oral mucositis is a common side effect of cancer therapies, particularly radiation therapy for head and neck cancer and various forms of chemotherapy. It commonly results in severe oral pain that can compromise the duration and success of cancer management. Hospitalizations are common because patients lose the ability to take anything by mouth due to severe pain and must have alimentation supported during this period. Pain management usually requires potent narcotic analgesia. Cancer therapy-related oral mucositis is commonly described as the most significant and debilitating acute complication associated with radiation therapy and chemotherapy. Until recently, cancer therapy-induced oral mucositis was thought to be a process involving the epithelium only. Evidence is building that the process of oral mucositis involves far more than just the epithelium, but includes multiple cellular processes of the submucosa as well. Many strategies have been evaluated to prevent oral mucositis, but the data is confusing since it is often conflicting. Therapy with the growth factor, KGF1, appears promising, as it is the only medication currently approved by the FDA. A multifaceted approach that targets the entire mucositis process will probably be needed to optimize overall prevention.

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*Key words:* oral mucositis, cancer, radiation therapy, chemotherapy

*Submitted for publication 3/31/05; accepted 5/2/05*

Oral mucositis is a common side effect of cancer therapies, particularly radiation therapy for head and neck cancer and various forms of chemotherapy. It commonly results in severe oral pain that can compromise the duration and success of cancer management. In the past, pain management to make the patient more comfortable has been the only universally accepted treatment. However, as other side effects of cancer therapy have been successfully managed (anemia, neutropenia, nausea and vomiting, etc.), researchers have turned their attention to the treatment and prevention of mucositis. This article will review the current concepts on the epidemiology, pathophysiology, prevention, and treatment of cancer therapy-related oral mucositis.

Oral mucositis is defined as oral mucosal change secondary to cancer therapy. It manifests first by thinning of oral tissues leading to erythema. As these tissues continue to thin, ulceration eventually occurs. It is at this stage that the primary symptom of severe debilitating oral pain is most severe.<sup>1</sup>

Severe mucositis is commonly seen in patients who are treated with myeloablative chemotherapy such as with hematopoietic stem cell transplant (HSCT) and those who receive radiation therapy for cancer of the oral cavity and surrounding structures.<sup>2,3</sup>

Though less common, oral mucositis also occurs secondary to chemotherapy for various solid tumors.

Severe mucositis can greatly complicate the management of cancer. It often leads to interruption of cancer treatment, which can compromise cure rates.<sup>4,5</sup> Hospitalizations are common because patients lose the ability to take anything by mouth due to severe pain and must have alimentation support during this period. Pain management usually requires potent narcotic analgesia. Patients who become neutropenic and develop severe mucositis are at greatly increased risk for the spread of oral organisms, through oral ulceration, into the systemic circulation, resulting in life-threatening systemic infection.<sup>6,7</sup> Mucositis has been shown to significantly lengthen hospital stays and increase the use of resources resulting in increased costs for patients receiving HSCT and patients receiving chemotherapy for solid tumors.<sup>8,9</sup> Increased hospitalization and feeding tube placement are also required more commonly for patients who receive radiation therapy and experience severe oral mucositis than for those who do not develop this side effect.<sup>10</sup> In summary, cancer therapy-related oral mucositis is commonly described as the most significant and debilitating acute complication associated with radiation therapy and chemotherapy.

Oral mucositis usually develops within seven to fourteen days after chemotherapy or radiation therapy is initiated. Mucositis secondary to radiation results from repeated tissue damage from multiple daily treatments. It begins to manifest at doses of 1000 to 2000 cGy (one to two weeks of therapy) and is limited to the field of radiation. Initial signs may include mucosal whitening due to transient hyperkeratinization followed by erythema, or erythema may occur first. Ulceration then occurs typically at doses over 3000 cGy. Following the end of radiation treatment, it requires three to six weeks for oral tissue to heal. In contrast, chemotherapy-related oral mucositis occurs on non-keratinized oral mucosal tissue only, and the most severe oral ulceration tends to occur when the patient reaches the nadir of their white blood cell count. Healing will occur within two to three weeks after chemotherapy is ended.<sup>1</sup>

The cancer patient's risk of developing oral mucositis is highly variable. As mentioned above, radiation therapy to the oral cavity and HSCT are associated with high rates of occurrence. Virtually all radiation patients who receive 5000 cGy or more will develop moderate to severe oral mucositis.<sup>1</sup> Severe oral mucositis ranges from 30 to 50 percent in patients receiving HSCT and is over 60 percent when total body irradiation is part of the regimen. With conventional chemotherapy including anthracycline-based regimens, taxane-based regimens, and platinum-based regimens, severe oral mucositis occurs in 1 to 10 percent of patients, but this can go as high as 66 percent when these agents are combined with 5 fluorouracil (5-FU). 5-FU alone typically causes severe oral mucositis in over 15 percent of patients. There is an increasing trend of combining chemotherapy with radiation to treat head and neck cancer. It is hoped that the combined therapy will result in better cancer response rates. However, as a side effect of this combined therapy, severe oral mucositis rates in these patients can go as high as 98 percent.<sup>8,11</sup>

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## Pathophysiology

Until recently, cancer therapy-induced oral mucositis was thought to be a process involving the epithelium only. Chemotherapy and radiation directly damage the basal cells of the mucosal epithelium, compromising the capacity of this tissue to regenerate itself. This results in epithelial thinning as no new cells are being developed at the basal layer and existing cells migrate to the surface and are exfoliated.

As more layers of cells are lost, the epithelium will become thinner and thinner, resulting in erythema initially and eventually ulceration. Radiation applied to the external surface of the epithelium causes DNA strand breaks in the basal epithelial cells. Chemotherapy causes basal cell damage when the drugs permeate to these cells from the blood vessels of the submucosal connective tissue.<sup>12-15</sup>

Evidence is building that the process of oral mucositis involves not only the epithelium, but includes multiple cellular processes of the submucosa as well.<sup>16</sup> Damage to the endothelium of submucosal blood vessels and to connective tissue occurs before damage to epithelial cells in irradiated oral mucosa.<sup>17</sup> A role for vascular endothelium and platelet function in oral mucositis is supported by evidence that inhibition of platelet aggregation can reduce mucosal toxicity.<sup>18</sup> The production of multiple pro-inflammatory cytokines has been shown to correlate with severity of oral mucositis, and blocking of these cytokines has shown some promise to lessen oral inflammation.<sup>17,19,20</sup> It is becoming clear that the development of oral mucositis is a dynamic process, but Sonis has divided mucositis into five stages to simplify its understanding. Sonis's five stages are initiation, primary damage response, signal amplification, ulceration, and healing.<sup>11,21</sup> These stages will be described below.

With radiation that is applied incrementally over seven weeks, these stages overlap. With chemotherapy, however, the tissue damage is delivered in a quick burst.

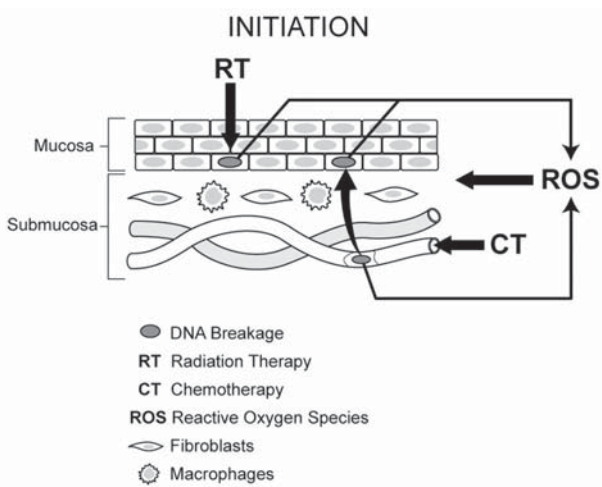
*Initiation.* Radiation and chemotherapy do cause DNA strand breaks and resultant direct basal cellular injury as described above. Concurrently, the primary initiators in a cascade of complimentary events contributing to oral mucositis appear to be the production of oxidative stress and reactive oxygen species (ROS), which are results of both radiation and chemotherapy and directly injure cells, tissues, and blood vessels.<sup>11,21</sup> Studies have shown that ROS are consistently produced when stomatotoxic agents are applied.<sup>22</sup> Also drugs that block or scavenge oxygen-free radicals have been shown in some cases to lessen mucosal damage from these same agents.<sup>23</sup> In addition to causing direct epithelial tissue damage, ROS also affect other tissues to stimulate transcription factors in subsequent phases. (See Figure 1.)

*Primary Damage Response.* Of the transcription factors activated by DNA strand breaks and ROS, nuclear factor- $\kappa$ B (NF- $\kappa$ B) appears to be the most

significant. It is activated by both radiation therapy and chemotherapy and results in upregulation of genes that lead to the production of a group of proinflammatory cytokines, including tumor necro-

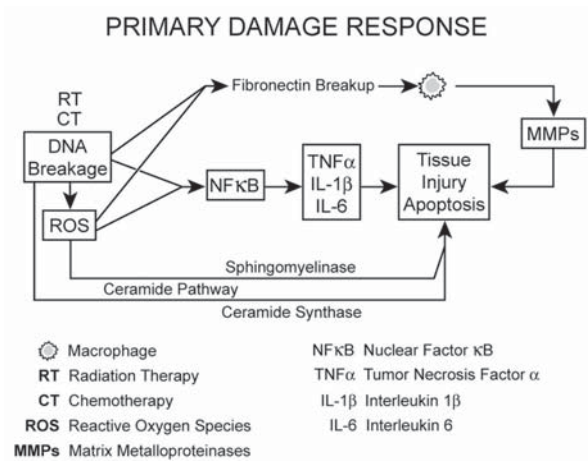
sis factor  $\alpha$  (TNF- $\alpha$ ), Interleukin 1 $\beta$  (IL-1 $\beta$ ), and Interleukin 6 (IL-6). Release of these cytokines results in tissue injury and apoptosis.<sup>24</sup> Other activity not related to DNA changes directly can lead to mu-

Damaging Stages of Cancer Therapy Oral Mucositis as Described by Sonis<sup>11,21</sup>



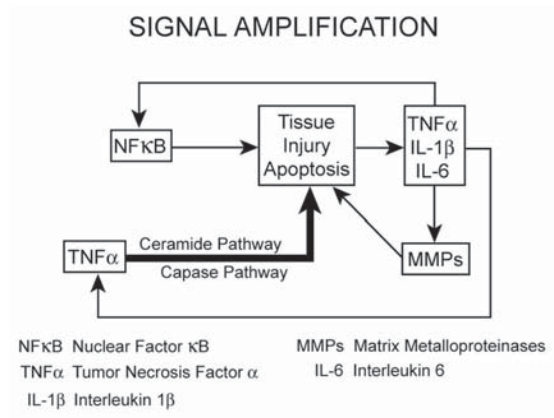
**Figure 1. Initiation**

Radiation therapy and chemotherapy cause DNA breakage in epithelial cells. This releases ROS, which cause direct epithelial tissue damage.



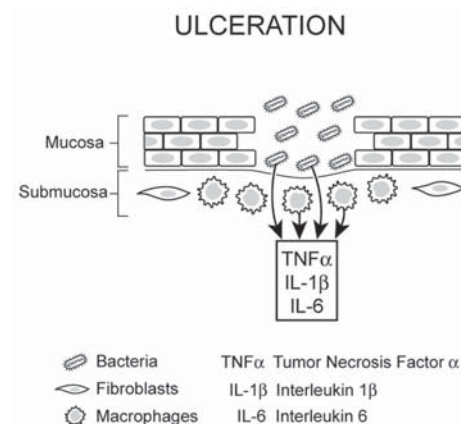
**Figure 2. Primary damage response**

DNA breakage and ROS from the Initiation stage activate NFκB, which leads to production of TNFα, IL-1β, and IL-6, which results in tissue damage and apoptosis. DNA breakage and ROS also stimulate the formation of sphingomyelinase and/or ceramide synthase, which activates the ceramide pathway leading to apoptosis. Fibronectin breakup, caused by DNA breakage and ROS, activates macrophages, which activates MMPs that cause direct tissue injury.



**Figure 3. Signal amplification**

Activities from the first two stages are combined so that proinflammatory cytokines amplify the damage initiated by radiation and chemotherapy. TNFα activates the ceramide and capase pathways leading to tissue damage. It also activates the transcription pathway mediated by NFκB. In a feedback loop there is increased production of TNFα, IL-1β, and IL-6. TNFα and IL-1β activate MMPs leading to direct tissue injury.



**Figure 4. Ulceration**

Epithelial integrity is lost. Colonizing microorganisms invade into the submucosa, which activates macrophages. Proinflammatory cytokines are released by organisms and macrophages. Damaging enzymes are then produced by inflammatory cells that move to the base of the ulcerated tissue.

cosal damage. Radiation and chemotherapy also hydrolyze the cell-membrane lipid sphingomyelin by stimulating the formation of sphingomyelinase or ceramide synthase, which activates the ceramide pathway leading to apoptosis.<sup>24-26</sup> Macrophages are activated by fibronectin breakup; this leads to stimulation of matrix metalloproteinases, which cause direct tissue injury or an increased production of TNF- $\alpha$ .<sup>27</sup> (See Figure 2.)

*Signal Amplification.* As the mucositis process continues, the activities from the first two stages are combined so that the proinflammatory cytokines amplify the mucosal damage initiated by radiation and chemotherapy. TNF- $\alpha$  activates the ceramide and caspase pathways leading to tissue damage and activates the transcription pathway mediated by NF- $\kappa$ B. In a feedback loop, these processes result in increased production of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6. TNF- $\alpha$  and IL-1 $\beta$  also activate matrix metalloproteinases leading to direct tissue injury as described previously.<sup>27,28</sup> (See Figure 3.)

*Ulceration.* All previous metabolic activity ultimately results in tissue ulceration, which is the most significant stage for the patient, as severe pain compromises function. As these patients are often neutropenic, ulcerated mucosa allows ingress of colonizing microorganisms from the mouth to the systemic circulation causing life-threatening sepsis. Also with ulceration, products from colonizing bacteria invade into the submucosal tissues. This activates macrophages, which results in the release of additional proinflammatory cytokines.<sup>29</sup> Damaging enzymes are then produced by inflammatory cells that move to the base of the ulcerated tissue.<sup>21</sup> (See Figure 4.)

*Healing.* The extracellular matrix initiates the healing phase of oral mucositis by signaling a renewal of epithelial cell proliferation and differentiation. Oral microbial flora is reestablished, and white cell counts return to normal. The tissue also appears to return to normal. However, epithelial tissue changes secondary to cancer therapy remain, and there is residual angiogenesis, increasing the patients' risk of oral mucositis with subsequent courses of anticancer therapy.<sup>11,21</sup>

There may be a genetic predisposition for developing oral mucositis related to cancer therapy. The same course of radiation therapy or chemotherapy can result in very different amounts of mucositis. One patient will need hospitalization and cessation of therapy to allow healing, while another experiences only mild discomfort. Animal studies have shown

that different mouse strains display very different mucosal responses to radiation therapy.<sup>30</sup> Single nucleotide polymorphisms (SNPs) have been identified that predispose a patient to drug toxicities when taking the chemotherapeutic agent methotrexate. Patients with these SNPs experience higher levels of oral mucositis than those where the SNPs are absent.<sup>31</sup> This is a fertile area for investigation. If oncologists could predict which patients were at high risk for mucositis by genetic testing, their therapy could be planned accordingly. As new strategies to prevent mucositis are developed, they could be targeted to the high risk patients only, reducing potentially costly prophylactic therapy.

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## Management and Prevention

There have been literally hundreds of clinical trials to evaluate different modalities to manage or prevent cancer therapy-induced oral mucositis. The data from these trials is often conflicting because the parameters used to evaluate efficacy vary greatly among studies. There are numerous scales used to grade the severity of mucositis in such studies.<sup>32-46</sup> They tend to focus on an investigator's objective findings of oral inflammation and/or ulceration or a patient's subjective reports of oral pain and functional compromise or a combination of the two. The most commonly used scales are the World Health Organization (WHO) scale and the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) scales.<sup>11</sup> These scales employ a combination of objective and subjective criteria. There is controversy about the need for the use of more objective scales in clinical trials. Some investigators, primarily dentists, feel that assessment of intraoral tissues is critical for an accurate assessment of mucositis severity.<sup>1</sup> Others, more commonly physicians, feel that patient symptoms (pain, ability to eat, etc.) are the only important parameters to evaluate and that tissue changes are not as important.<sup>47,48</sup> Subjective evaluations may give an accurate assessment of patient function, but do not take into account the potential for oral organisms to cause systemic infection through the oral tissue damage associated with mucositis. Therefore, objective evaluations may be more important than some investigators realize. Most current investigators are trying to standardize the rating scales used in clinical trials. It appears that the WHO scale and the NCI-CTC scales will remain standards for the immediate future.<sup>40,41</sup>

Pain control is a critical component of any mucositis management strategy because this is often the primary patient complaint. Pain control is initiated with topical analgesics and followed with increasingly potent systemic medication. However, the detailed management of cancer pain is beyond the scope of this article. The reader is referred to the monograph "Oral Health in Cancer Therapy" for a detailed discussion of this topic.<sup>49</sup>

As mentioned above, there are conflicting results for a large number of mucositis management and prevention strategies. It is impossible to cover all therapies in this review. However, a representative sample will be presented to give the reader a sense of the large variety of therapies studied. These are listed in Table 1.

**Oral Hygiene.** Oral care to remove potential sources of infection provided in conjunction with cancer therapy is necessary to prevent serious complications, including rampant decay and osteoradionecrosis with radiation therapy and potentially life-threatening infections and bleeding with chemotherapy.<sup>49</sup> However, the data on the effectiveness of oral care in reducing or preventing mucositis in these patients is less clear. Several studies have shown a reduction in oral mucositis in patients who received oral care to remove sources of infection before and during their cancer therapy.<sup>50-52</sup> Other studies have shown no such change.<sup>53,54</sup> Two different studies in children showed that standardized oral care protocols reduced mucositis in one group and oral pain in the other.<sup>55,56</sup> Many investigators feel oral care with cancer therapy is beneficial, but the effect on mucositis is yet to be proven.

**Infection Prevention.** It has been postulated that infection may play a role in the severity of cancer therapy oral mucositis, and this area has been investigated extensively. Two studies have shown that use of a topical antimicrobial lozenge containing polymyxin, tobramycin, and amphotericin B reduced oral mucositis with radiation therapy.<sup>57,58</sup> Chlorhexidine oral rinses have been shown in several studies to reduce oral mucositis, particularly in patients receiving HSCT and radiation.<sup>59,60</sup> However, other studies in these same types of patients have shown no effect.<sup>61,62</sup> As mentioned above, mucositis appears to predispose neutropenic patients receiving chemotherapy to systemic streptococcal infections.<sup>6</sup> However, clindamycin prophylaxis was not able to prevent these infections in HSCT patients.<sup>63</sup> Herpes simplex virus (HSV) reactivation is common in patients receiving chemotherapy and is as high as 60

**Table 1. Mucositis prevention therapies**

1. Oral Hygiene
2. Infection Prevention
  - a. Antimicrobial Lozenges
  - b. Chlorhexidine
  - c. Clindamycin
  - d. Acyclovir, Valacyclovir, Famcyclovir
  - e. Fluconazole, Clotrimazole, Nystatin
3. Anti-Inflammatory Agents
  - a. Dinoprostone
  - b. Misoprostol
  - c. Prednisone
  - d. Pentoxifylline
  - e. Benzylamine
4. Reactive Oxygen Species Inhibitors
  - a. Amifostine
  - b. N-acetylcysteine
  - c. Manganese Superoxide Dismutase
5. Salivary Function Modifiers
  - a. Propantheline
  - b. Pilocarpine
6. Azelastine
7. Cryotherapy
8. Glutamine
9. Coating Agents
  - a. Sucralfate
  - b. Hydroxypropylcellulose Gel
  - c. Polyvinylpyrrolidone and Sodium Hyaluronate
10. Laser Therapy
11. Growth Factors
  - a. Epidermal Growth Factor (EGF)
  - b. Granulocyte Colony Stimulating Factor (GCSF)
  - c. Granulocyte Macrophage Colony Stimulating Factor (GMCSF)
  - d. Transforming Growth Factor Beta 3 (TGFb3)
  - e. Interleukin 11 (IL-11)
  - f. Fibroblast Growth Factors (FGFs)
    - i. Keratinocyte Growth Factor 1 (KGF1, FGF7)
    - ii. Fibroblast Growth Factor 10 (FGF10)
    - iii. Fibroblast Growth Factor 20 (FGF20)

percent in those receiving HSCT.<sup>64</sup> HSV does not cause mucositis, but reactivation results in a more severe and longer lasting course of ulceration than seen with HSV reactivation in immunocompetent individuals.<sup>65</sup> HSV reactivation can be largely prevented with acyclovir, famcyclovir, or valacyclovir targeted at patients who prove to be seropositive prior to receiving conventional chemotherapy.<sup>66</sup> It is therefore important to evaluate these patients carefully and to maintain a high degree of suspicion for reac-

tivation of HSV. Candida organisms do not appear to be involved in the etiology of mucositis, but should be borne in mind to lessen the potential for the spread of systemic infection through ulcerated tissue. Fluconazole and clotrimazole prophylaxis have been shown to reduce candidiasis in cancer patients.<sup>67,68</sup> Nystatin suspension prophylaxis is not effective in the same patients, even though it is still commonly used in many cancer centers.<sup>69</sup>

*Anti-Inflammatory Agents.* As discussed in the pathophysiology section above, the inflammatory response clearly plays a significant role in the initiation and progression of cancer therapy-induced oral mucositis. Therefore, approaches to block various stages of inflammation have been proposed as potentially promising therapies. Prostaglandins and steroids have been evaluated to reduce mucositis. These include dinoprostone (prostaglandin E2), misoprostol (prostaglandin E1), and prednisone. The impact on mucositis was not significant.<sup>70,71</sup> Pentoxifylline has been shown to reduce production of TNF $\alpha$  but has not been successful in reducing mucositis in patients taking chemotherapy.<sup>72-74</sup> Benzydamine is a non-steroidal anti-inflammatory rinse that has been shown to inhibit TNF $\alpha$  as well.<sup>75</sup> It has been shown to be effective in reducing oral mucositis and resultant oral pain associated with radiation therapy.<sup>76</sup> Benzydamine is available in Canada and Europe, but is not approved by the FDA for use in the United States.

*ROS Inhibitors.* Since ROS production is associated with both radiation therapy and chemotherapy-induced oral mucositis, inhibition of these molecules would appear to be a promising strategy. Amifostine, an ROS inhibitor, was developed to protect U.S. soldiers from the effects of radiation. It lessens DNA strand breaks after radiation therapy; may protect endothelium, salivary glands, and connective tissue; and has been shown to reduce IL-6 and TNF $\alpha$  in the blood of cancer patients.<sup>77,78</sup> There is conflicting data on its ability to reduce mucositis in patients receiving head and neck radiation or chemotherapy, and both positive and negative results have been reported.<sup>79-82</sup> Currently, amifostine is approved by the FDA only to reduce the severity of xerostomia after radiation therapy and to reduce renal toxicity with cisplatin chemotherapy. Other ROS inhibitors that may be promising for further investigation include N-acetylcysteine, manganese superoxide dismutase, and benzydamine.<sup>76,83</sup>

*Salivary Function Modifiers.* If chemotherapeutic medications excreted in saliva contribute to oral mucositis, then inhibiting salivary function could

reduce this complication. Propantheline, an anticholinergic drug, has been shown to reduce the severity and frequency of oral mucositis in patients receiving etoposide chemotherapy.<sup>84,85</sup> Conversely, salivary stimulation may actually speed the healing of mucositis because epidermal growth factor (EGF) is present in saliva. EGF plays a critical role in normal wound healing.<sup>1</sup> This will be discussed in more detail below.

*Azelastine.* Azelastine is a compound that has been shown to possibly reduce the respiratory burst activity of neutrophils and reduce cytokine release from lymphocytes. It was shown to reduce the severity of oral mucositis in patients receiving radiation and chemotherapy for oral cancer.<sup>86</sup>

*Cryotherapy.* It has been proposed that if blood flow to the oral mucosa could be decreased during chemotherapy administration, then this tissue would be exposed to less drug, resulting in less mucositis. This can be accomplished by having patients suck on ice chips before and during treatment and is termed cryotherapy. Cryotherapy has been shown to reduce oral mucositis in patients taking 5-FU chemotherapy in two clinical trials.<sup>87,88</sup>

*Glutamine.* Glutamine is an essential amino acid that is critical to the regulation of protein synthesis, respiratory fueling, and nitrogen shuttling. It has been shown to reduce gastrointestinal mucositis in animals receiving chemotherapy. Results in human trials have been mixed. AES-14, which is glutamine in a vehicle that greatly increases its uptake, has recently been shown to decrease grade 2 or higher mucositis in patients receiving chemotherapy for solid tumors.<sup>89</sup>

*Coating Agents.* The goal of coating agents is to cover the ulcerated tissue of mucositis, thereby acting like an intraoral bandage. Some may contain topical anesthetics, which are short acting, but the effective function is long-term coverage. Sucralfate suspension is thought to adhere to areas of gastrointestinal mucosa ulceration, thus creating a surface barrier, and is used in the management of these ulcers. It was proposed that sucralfate suspension would adhere to areas of oral ulceration as well. However, results in clinical trials have been mixed.<sup>90-93</sup> Hydroxypropylcellulose gel provides good adherence and coverage to localized areas of oral ulceration. It was evaluated as a coating agent for mucositis in patients receiving chemotherapy. Oral pain was reduced, and duration of adherence was commonly seen for at least three hours.<sup>94</sup> The application of this material in this patient population is technique sen-

sitive, and this has reduced its use and effectiveness. Polyvinylpyrrolidone/sodium hyaluronate gel has been shown to reduce oral mucositis in two preliminary studies.<sup>95,96</sup>

*Laser Therapy.* Low energy laser therapy has been proposed as a treatment to prevent or lessen oral mucositis. It is felt that the laser's effect on mitochondria or on ROS would provide this protection. Initial studies are encouraging.<sup>97,98</sup>

*Growth Factors.* Currently, the use of growth factors is the most exciting area in the quest to find a prevention for cancer therapy mucositis. There are numerous types of growth factors, and they are largely molecules that are normally produced in minute quantities by a variety of cells. They can be genetically produced in much larger quantities to deliver the appropriate molecule at the targeted time. The primary goal of all growth factors is to stimulate cells that will counteract the negative side effects of chemotherapy and radiation. Epidermal growth factor (EGF) is a molecule present in saliva that promotes wound healing. Radiation therapy results in a reduction of salivary EGF. Conflicting studies have shown that higher levels of salivary EGF are associated with more mucositis and less mucositis.<sup>99,100</sup> EGF mouthwash produced a delay in onset and a reduced severity in recurrent ulceration in patients receiving chemotherapy.<sup>101</sup> Two hematopoietic growth factors—granulocyte colony stimulating factor (GCSF) and granulocyte macrophage colony stimulating (GM-CSF)—have been employed extensively to lessen mucositis. These drugs stimulate neutrophil production. It is felt that by reducing neutropenia with these drugs during chemotherapy, infections will be lessened, and if infections are a cofactor for mucositis, this will be reduced as well. Results have been conflicting.<sup>102-105</sup> Transforming Growth Factor-beta-3 and Interleukin-11 have also been studied with mixed results.<sup>1,106-108</sup> The fibroblast growth factors (FGFs) appear to be the most promising of the growth factors. Keratinocyte growth factor (KGF) is the most studied of these growth factors and is also known as KGF1 or FGF7. KGF1 (palifermin is its generic name) has been shown to reduce oral mucositis in patients receiving HSCT, and is the first compound approved by the FDA for this indication. Not only did it reduce grade 3 and grade 4 mucositis, but it led to reduced duration of mucositis, reduced oral pain, reduced use of narcotic analgesia, and reduced use of total parenteral nutrition.<sup>48,108</sup> KGF1 stimulates the mucosal epithelium and probably improves the ability of this epi-

thelium to withstand the toxicity of chemotherapy and may also upregulate anti-inflammatory cytokines and downregulate proinflammatory cytokines.<sup>109</sup> It is being currently evaluated to prevent mucositis in other at-risk populations. Two other FGFs, FGA10 and FGF20, have been studied in animals and are in clinical trials.<sup>21</sup>

In summary, there has been extensive evaluation of multiple preventive strategies for oral mucositis. Often the results are confusing, because the data from these trials is conflicting. It appears that since oral mucositis is a multifaceted complication, it will require a multifaceted approach. For example, the encouraging results with parenteral KGF1 may have provided us with some early knowledge about the role of growth factors in the prevention of oral mucositis. As other molecules are tested, we will hopefully learn more. Topical therapies, such as glutamine, that provide essential nutrients needed with cancer therapy, have shown promise. Oral care and oral infection prevention have not been proven to prevent oral mucositis, but may prevent the spread of life-threatening infection from the oral cavity into the systemic circulation. In the future, these and other strategies may need to be combined to effectively lessen and/or prevent the ravages of cancer therapy-induced oral mucositis.

As the above therapies are being developed and tested, it will become even more critical for dental professionals, as experts of the oral cavity, to be involved in evaluating these modalities and providing oral care for cancer patients. Therefore, it will be necessary to provide comprehensive training on oral complications of cancer therapy for dental professionals. This is probably best accomplished at the postdoctoral level in general dentistry or specialty residencies and focused continuing education programs where patient care experience can be obtained. The final goal would be to have an adequate cadre of dental professionals to support oncologists in the oral management of these patients.

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