Oncology Pharmacotherapy: Modulation of Chemotherapy-Induced Mucositis

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Introduction

Inflammation of the mucous membranes of the gastrointestinal tract, or mucositis, can impair the quality of life and treatment of patients with cancer. Mucositis is a particularly common problem in this population due to the use of chemotherapy and radiation with curative or palliative intent. Many patients who receive standard-dose chemotherapy experience some degree of mucositis, while most patients treated with high-dose chemotherapy with stem cell rescue experience severe complications. When the mucous membranes are exposed to ionizing radiation, inflammatory changes are expected. Combined modality therapy consisting of concurrent radiation and chemotherapy can produce highly symptomatic stomatitis (in patients with head and neck cancer) or esophagitis (in patients with small cell lung cancer). Mucositis can be a dose-limiting complication that can interfere with attempts to increase the dose intensity of cancer therapy. This article reviews the clinical aspects of mucositis and focuses on efforts to discover effective prophylactic interventions.

Clinical Presentation

Clinicians tend to restrict the definition and evaluation of mucositis to the oropharynx and lips, perhaps because of the easy accessibility of these areas for evaluation. Chemotherapy can affect all mucous membranes, however, and evaluation should include the eyes, nose, esophagus, vagina, bladder, and, entire gastrointestinal tract.

Oral mucositis from chemotherapy usually is preceded by the sensation of dry mouth and lips starting several days after administration of chemotherapy. If the complication progresses, the lips become chapped and whitish patches develop in the mucocutaneous junctions of the oropharynx. These patches usually are painful and can interfere with eating. If no complication or extension occurs, healing takes place over a period ranging from several days to several weeks.[1] Evidence for mucositis in less visible sites includes dysphagia in the esophagus and abdominal tenderness and diarrhea in the gastrointestinal tract. Involvement of the nasal passages is manifested by dryness and irritation, and pericoronitis involvement is indicated by dryness and excess tearing. Cough may reflect bronchial irritation. Finally, severe mucositis can produce a breakdown in the barrier component of the immune system, allowing for bacterial translocation from the gastrointestinal tract to the bloodstream.[1,2] In neutropenic patients, such bacteremia can be life threatening.

Pathogenesis

Chemotherapy can damage the oral and gastrointestinal mucosa through direct or indirect toxicity. The mechanism for direct mucositis is nonspecific cell kill of rapidly dividing basal epithelial cells that results in epithelial thinning, inflammation, decreased cell renewal, and ultimately ulceration. These painful lesions also produce an increased risk for local and systemic infection.

Indirect mucotoxicity is a byproduct of chemotherapy-induced myelosuppression. Profound granulocytopenia permits oral infections by Gram-negative bacilli, Gram-positive cocci, fungi such as Candida species, and viruses (particularly Herpes simplex). These infections usually occur at the site of direct mucositis or other oral trauma. A patient with a platelet count of 10 x 10^9 to the ninth per liter or less is at risk for spontaneous bleeding from oropharyngeal ulcerations. Indirect mucotoxicity is associated with the white blood cell count nadir following chemotherapy and most often occurs 12 to 14 days after drug administration.[1,2]

Direct mucotoxicity is the common side effect of a variety of chemotherapeutic agents. Those agents that can produce direct mucositis at standard doses include antimetabolites such as methotrexate, fluorouracil, and cytarabine; alkylating agents such as mechlorethamine, cyclophosphamide, and ifosfamide; anthracyclines such as doxorubicin and idarubicin; and natural products such as bleomycin and dacarbazine.[1,2] This toxicity can be dose- and schedule-related, which is evident by the severity of mucositis associated with high-dose chemotherapy with stem cell rescue. Some drug combinations (eg, cisplatin and continuous infusion fluorouracil for squamous cell head and neck cancer) are particularly predisposed to produce mucositis out of proportion to the level of hematologic toxicity.[1] Factors indicating high risk for mucositis include age younger than 20 years, preexisting periodontal disease, presence of hematologic or head and neck malignancies, and acquired immunodeficiency syndrome.[2] The risk is compounded by concomitant radiation to mucosal areas. Mucositis may be more common in women or in white patients. The Eastern Cooperative Oncology Group trial E2296 of adjuvant fluorouracil with leucovorin in patients with resected colon cancer reported a 26% incidence of grade 2 or greater toxicity in men compared with 36% in women, as well as a 32% incidence of pain in white patients compared with 22% in black patients and 24% in other minorities (unpublished data).

Table 1. National Cancer Institute Common Toxicity Criteria for Grading of Stomatitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Painless ulcers, erythema, or mild soreness</td>
</tr>
<tr>
<td>2</td>
<td>Painful erythema, edema, or ulcers but ability to eat</td>
</tr>
<tr>
<td>3</td>
<td>Painful erythema, edema, or ulcers and inability to eat</td>
</tr>
<tr>
<td>4</td>
<td>Parenteral or enteral support</td>
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</table>

Quantification of Mucositis

The lack of a standard grading scale for severity is one of the challenges of interpreting the literature pertaining to mucositis. Criteria that are commonly used in the United States to grade stomatitis are presented in Table 1. An accurate evaluation of a patient, in which the mucositis grade, the severity of mucosal pain, and the adequacy of oral intake are determined, will lead to appropriate diagnostic and therapeutic interventions.

Management Principles

A well-established prophylaxis for direct mucositis currently is unavailable, other than a prescription of suboptimal doses of chemotherapy, a downward dose modification in subsequent treatment courses following toxicity, or the use of specific antidotes such as leucovorin after moderate-dose or high-dose methotrexate[3] (Table 2). Prophylactic chlorhexidine[4-6] and nystatin or clotrimazole[7] may be given to reduce the risk of indirect mucotoxicity from bacteria and fungi in patients at high risk for greater than grade 2 or prolonged toxicity. Prophylactic fluconazole reduces the risk of oropharyngeal candidiasis at the risk of the development of resistance.[7] Herpes simplex virus-antibody-positive patients undergoing high-dose chemotherapy with stem cell rescue should be given acyclovir 250 mg/m^2 intravenously every eight hours for prevention of mucocutaneous infections from viral reactivation.[8]

A patient with stomatitis should follow a regular mouth-care routine of rinsing the oral cavity with distilled water or sterile normal saline solution for a full minute at least four times per day, followed by gently brushing the teeth, gums, and tongue with a fluoride toothpaste. Patients at high risk for neutropenia and thrombocytopenia should use disposable foam sticks instead of toothbrushes to reduce possible pain, bleeding, and transient bacteremia that can occur following brushing. Acidic, salty, spicy, and coarsely textured foods should be avoided.
Treatment of mucositis is primarily supportive. Patients with low to moderate pain can be managed with local anesthesiology. Most institutions have their own version of "magic mouthwash," a combination product of the topical treatment of mild opharyngeal pain. The version at our institution consists of viscous lidocaine, diphenhydramine, Maalox, 70% sorbitol, and orange flavoring. Both viscous lidocaine and diphenhydramine have local anesthetic properties, while the aluminum hydroxide component of Maalox has a potent inhibitor of the enzyme orotidylate decarboxylase. This results in intracellular accumulation of orotic acid that competes with fluorouracil for orotate phosphate, is a potent inhibitor of the enzyme orotidylate decarboxylase. This results in intracellular accumulation of orotic acid that competes with fluorouracil for orotate phosphoribosyltransferase. This competitive inhibition of fluorouracil conversion to fluorouracil monophosphate may be responsible for reducing fluorouracil toxicity. Theoretically, this also would be expected to reduce efficacy if administered systemically.\[16\]

Topical Prophylactic Agents

Sucralfate

Sucralfate is a nonabsorbable, basic aluminum salt of sulfated sucrose indicated for the treatment of peptic ulcer disease. Sucralfate forms an iononic bond to proteins in ulcerations, which produces a protective barrier that promotes healing. In addition, local production of the cytoprotectant prostaglandin E2 is stimulated.\[2\] Pfeiffer et al \[12\] performed a randomized, double-blind cross-over study of patients receiving a cisplatin/fluorouracil regimen for various solid tumors. Patients were instructed to swish and expectorate or swallow sucralfate suspension (1 g) or placebo four times per day for 14 days starting on the first day of chemotherapy. With the second course of chemotherapy, patients were given the alternative solution. Seventeen of 40 patients were not evaluable, primarily due to intolerance to the rinsing procedure. Of the remaining 23 patients, the objective evaluation revealed less mucositis with the sucralfate treatment (P = 0.04). Patient preference was not statistically significant (P = 0.06) in favor of sucralfate. This study demonstrated a modest benefit for sucralfate suspension in patients who were able to tolerate the regimen.

Prostaglandin E2

Prostaglandin E2 (PGE2), a naturally occurring substance with alleged cytoprotective activity, has been reported to be beneficial in healing gastric ulcers and chronic leg ulcers.\[2\] Porteller et al \[13\] studied 10 patients with oral and maxillary tumors who were given 0.5 mg of local PGE2 twice times daily concurrently with combined radiation and chemotherapy (primarily with fluorouracil and mitomycin C). These patients were compared with 14 historical control patients. Eight of the 10 control patients completed the treatment courses and were evaluable. None suffered from severe mucositis, while six of the historical control patients did experience severe mucositis. Blood samples failed to demonstrate any evidence of significant systemic absorption. This study is inconclusive due to the lack of a randomized control group.

Labar et al \[14\] performed a controlled, double-blind trial of 60 leukemic patients undergoing BMT with total body irradiation and cyclophosphamide or cyclophosphamide and busulfan. Patients were randomized to placebo or 0.5 mg tablets of PGE2. Those receiving PGE2 were instructed to dissolve tablets in the mouth three times daily from day 7 through day +21. No significant difference was found in the incidence of grade 3 or grade 4 mucositis between the treatment group (55%) and the control group (52%). The duration of severe mucositis also was nearly identical in both groups. Herpes simplex virus (HSV) reactivation was greater in the PGE2 group (71%) than the placebo group (38%), which was unexpected. Any beneficial effect of PGE2 may have been obscured by HSV-induced mucositis. None of these patients received acyclovir prophylaxis for HSV. In summary, PGE2 does not appear to have significant activity following BMT and may predispose to HSV reactivation.

Allopurinol

Allopurinol, a xanthine oxidase inhibitor, has been studied for both prophylaxis and treatment of fluorouracil-induced mucositis. Two primary mechanisms have been proposed for such activity: nonspecific free-radical scavenging\[15\] and specific inhibition of fluorouracil activation. A metabolic product of allopurinol, 1-oxypurinol-5'-phosphate, is a potent inhibitor of the enzyme orotidylate decarboxylase. This results in intracellular accumulation of orotic acid that competes with fluorouracil for orotate phosphoribosyltransferase. This competitive inhibition of fluorouracil conversion to fluorouracil monophosphate may be responsible for reducing fluorouracil toxicity. Theoretically, this also would be expected to reduce efficacy if administered systemically.\[16\]

Based on this hypothesis, Clark and Slevin\[17\] reported on six patients with colorectal cancer and histories of fluorouracil-induced mucositis. All received the next course of fluorouracil bolus therapy at the same dosage along with allopurinol mouthwash. Patients were instructed to swish and expectorate 15 to 20 mL of a 1 mg/mL solution immediately after the fluorouracil infusion and again at one, two, and three hours thereafter only on the days of treatment. An improvement in mucositis grade was noted in all six patients. In another study, the effects of allopurinol mouthwashes were analyzed in 16 patients who had gastrointestinal tumors and who also had previously developed mucositis as a result of fluorouracil monotherapy (800 mg/m squared per day by continuous infusion for five days). This uncontrolled group received 16 mg/mL of allopurinol solution. Patients were instructed to swish for five minutes and then expectorate four to six times per day for at least six days, beginning with day 1 of the fluorouracil infusion. A reduction of mucositis grading and an inability to swallow food was noted in all patients. Since a 16-fold higher concentration of allopurinol was used, the possibility of systemic absorption must be considered. These promising preliminary results were not confirmed by the controlled trial of Loprinzi and colleagues.\[19\] Prior to their study, they verified that their 1 mg/mL allopurinol solution did not produce detectable blood levels when used as a mouthwash. Seventy-seven patients were entered on a trial of fluorouracil vs leucovorin bolus injections for colorectal cancer. Only four of these patients received fluorouracil monotherapy. Patients were randomized to receive allopurinol or placebo mouthwash solutions and were instructed to first coat their lips with the mouthwash, then swish 20 mL for 30 seconds and expectorate immediately following fluorouracil administration and at one, two, and three hours thereafter. During their second course of therapy, 20 patients were given the alternative mouthwash. No clinically or statistically significant benefit of the allopurinol solution was detected by this trial. In fact, a trend was noted toward worsened mean physician-graded (P = 0.07) and patient-graded (P = 0.15) mucositis. This trial indicates that allopurinol is ineffective in preventing mucositis in patients taking fluorouracil in combination with leucovorin.

Due its antioxidant properties, allopurinol has been investigated for the prevention of mucositis and enteritis for high-dose thiopeta, mitoxantrone, and paclitaxel with stem cell rescue in breast cancer patients.\[20\] Sixteen patients receiving 300 mg of allopurinol orally twice a day from day -9 through day -2 were compared with 12 historical patients following the same regimen. No statistically significant differences were detected in incidence, onset, or duration of severe mucositis, duration of diarrhea, or requirements for parenteral nutrition or narcotic analgesics. The antioxidant effects of allopurinol with currently studied regimens do not produce clinically significant effects.

Systemic Prophylactic Agents

Beta-Carotene

Beta-carotene, or provitamin A, has been studied in patients with cancer due to its antioxidant properties and safety. In a study of 20 patients with advanced squamous cell carcinoma of the mouth,\[21\] patients were hospitalized and treated with daily fractions of telecobalt radiation therapy in combination with vincristine, bleomycin, methotrexate, and leucovorin. All patients were smokers but reportedly refrained from smoking during the trial. Patients were randomized to a standard diet with or without a magic mouthwash, a combination product of the topical treatment of mild opharyngeal pain. The version at our institution consists of viscous lidocaine, diphenhydramine, Maalox, 70% sorbitol, and orange flavoring. Both viscous lidocaine and diphenhydramine have local anesthetic properties, while the aluminum hydroxide component of Maalox has a potent inhibitor of the enzyme orotidylate decarboxylase. This results in intracellular accumulation of orotic acid that competes with fluorouracil for orotate phosphoribosyltransferase. This competitive inhibition of fluorouracil conversion to fluorouracil monophosphate may be responsible for reducing fluorouracil toxicity. Theoretically, this also would be expected to reduce efficacy if administered systemically.\[16\]
beta-carotene supplementation. Beta-carotene was given initially at doses of 250 mg daily for 21 days and then at 75 mg daily for the remainder of the therapy. The control group did not receive a placebo. At the conclusion of the trial, the study patients suffered 22 patient-weeks of severe mucositis compared with 38 patient-weeks in the control group (P=0.025). Remission rate was not affected by treatment group. These preliminary findings indicate that further investigation of this safe, inexpensive agent is needed.

Propantheline

Mucositis is a dose-limiting toxicity of high-dose etoposide as a component of BMT conditioning regimens. Ahmed et al[22] speculated that etoposide in the patients’ saliva was partly responsible for the stomatotoxicity. In their study of 12 patients with hematologic malignancies receiving allogeneic BMT with etoposide 1800 mg/m² at a continuous infusion over 24 hours in combination with high-dose cyclophosphamide and carmustine, the patients were randomized to receive 30 mg of propantheline or placebo every six hours for six doses. Mucositis occurred in two of six propantheline patients vs five of six placebo patients (P=0.06). Average severity was less in the treatment arm (grade 1) than in the control arm (grade 2) (P=0.05). The relatively low mucotoxicity of this regimen was evident in that no patients required narcotic analgesia. This study was restricted in importance by the small sample size and minimal data reported.

Leucovorin

Leucovorin, or folic acid, in combination with urinary alkalinization and hydration is well established as a rescue agent to reduce mucositis and myelotoxicity of high-dose methotrexate (100 to 12,000 mg/meter squared).[3] Leucovorin attenuates methotrexate toxicity by acting as a folic acid analog that does not require activation by dihydrofolate reductase. The timing of leucovorin dosing is critical to avoiding the target malignant cells. Lower doses of methotrexate frequently are used in combination with cyclophosphorine to prevent acute graft-vs-host disease in patients following allogeneic BMT. These patients are at higher risk of mucositis due to their high-dose conditioning regimens.

Russell et al[23] reported on the addition of leucovorin to their allogeneic BMT regimen. Sixty-nine adult patients received primarily high-dose cyclophosphamide in combination with total body irradiation or busulfan for various hematologic malignancies. Standard cyclophosphamide and methotrexate (15 mg/meter squared on day 1, 10 mg/meter squared on days 2-6) with leucovorin rescue was started 24 hours after each dose of methotrexate and was continued every six hours until 12 hours before the next dose of methotrexate. After day +11, leucovorin was continued until engraftment. No cases of severe mucositis (grade 3 or grade 4) were reported, and there was no evidence of increased graft-vs-host disease. A controlled clinical trial addressing the use of low-dose leucovorin in allogeneic BMT would be of value.

Pentoxifylline

Pentoxifylline (PTX) is a hemorheologic agent indicated for treatment of intermittent claudication. PTX has been shown to reduce the production of tumor necrosis factor alpha (TNF-alpha) possibly by inhibiting TNF-messenger RNA transcription. Since elevated TNF-alpha plasma levels have been associated with many BMT complications, PTX was worthy of research. In addition, PTX stimulates vascular endothelial production of prostaglandins PGII2 and PGE2, which would be expected to enhance local-regional blood flow and promote thrombolysis.[24]

Bianco et al[25] reported data on oral PTX in patients with hematologic malignancies undergoing BMT. Three groups consisting of ten patients each were given 400 mg of PTX at escalating levels of three times daily (1200 mg/day), four times daily (1600 mg/day), and five times daily (2000 mg/day) from day -10 through day +100 following transplantation. In a comparison of these patients to a historical control of 20 patients, adverse effects of PTX were limited to mild gastrointestinal symptoms. Results showed a significant reduction in average days of intravenous morphine (3.7 vs 18.7), days of total parenteral nutrition (24 vs 35), incidence of hepatic dysfunction, renal insufficiency, and moderate to severe graft-vs-host disease.

Stockschlader et al[26] attempted to duplicate this study with an intravenous formulation of PTX in allogeneic BMT recipients. Increasing levels of dosage were studied as continuous intravenous infusion beginning on day 1 of the conditioning regimen: 0.5 mg/kg per hour (two patients), 0.75 mg/kg per hour (four patients), and 1.0 through 1.25 mg/kg per hour (25 patients). After recovery from transplant-related gastrointestinal toxicity, patients were converted to oral PTX at either 1600 mg/day if body weight was less than 70 kg or 2000 mg/day if body weight was more than 70 kg. Intravenous PTX was well tolerated, with the exception of one patient with restlessness and tachycardia following an excessively rapid infusion. However, the PTX regimens showed no benefit over the control group. In fact, the incidence of severe mucositis (100% vs 68%) and hyperbilirubinemia (greater than 1.5 mg/dL: 84% vs 30%) were significantly elevated in the treatment group.

Atall and colleagues[27] conducted a prospective, randomized trial of 140 patients to establish the role of PTX in the prevention of BMT complications. Patients were randomized to receive (n=70) or not receive (n=70) 400 mg of PTX orally four times daily from day -8 through day +100 among autologous and allogeneic BMT recipients with hematologic malignancies. No effect was observed on the incidence of mucositis requiring morphine sulfate, the mean number of days of intravenous morphine, graft-vs-host disease, or organ toxicities.

Further evidence for the lack of benefit of PTX in the BMT setting was provided by van der Jagt et al.[28] They performed an unblinded, historical, controlled study of 400 mg of PTX orally every four hours from day -10 through day +35 in BMT patients. They also found no benefit of PTX or any other BMT-related complication.

Lisofylline

Research is underway on the effect of lisofylline (CT-1501R), a metabolite of PTX with superior TNF-alpha activity, on complications of BMT. Prior to ongoing clinical trials, lisofylline had not been administered directly to human subjects. However, Bianco et al[28] reported on the status of 15 patients following allogeneic BMT for hematologic malignancies who were receiving 2000 mg/day of PTX in combination with 1000 mg/day of ciprofloxacin. The treatment group required fewer days of morphine for mucositis (2.8 ± 3.9 days) when compared with 10 patients in a historical control group (12.3 ± 7.1 days). This effect was attributed to elevated blood levels of CT-1501R following cytochrome P450 inhibition by ciprofloxacin.

Filgrastim

Filgrastim, or granulocyte-colony stimulating factor, is a recombinant protein approved for the prevention of febrile neutropenia following myelosuppressive chemotherapy. A role for filgrastim in the prevention of mucositis was not originally hypothesized. Gabrilove et al[29] reported a 33% reduction in the overall incidence of mucositis following chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin for transitional cell bladder cancer. This was an incidental finding in this dose-escalation trial, and further trials have not supported this supposition. Bronchud and colleagues[30] studied the use of filgrastim at doses of 10 micrograms/kg per day for seven days followed by 5 micrograms/kg per day for four days to allow dose escalation of doxorubicin in patients with advanced breast and ovarian cancers. Filgrastim permitted higher dosage by reducing the duration and severity of neutropenia. However, no protective effect on mucositis was observed. Pettengell et al[31] conducted a randomized, open-label trial of filgrastim 230 micrograms/meter squared vs no growth factor in 80 patients with non-Hodgkin’s lymphoma undergoing intensive chemotherapy with vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin. The use of filgrastim resulted in fewer treatment delays secondary to febrile neutropenia, which resulted in mucositis as the most frequent cause of delay in the filgrastim-treated group. No difference in the incidence of grade 3 or grade 4 mucositis was detected between the two groups. Overall, filgrastim does not appear to have a clinically significant protective effect on the epithelium.

Nonpharmacologic Prophylaxis

Cryotherapy

Mahood et al[32] investigated a novel approach to the prevention of mucositis in patients receiving fluorouracil and leucovorin chemotherapy. A total of 95 patients were randomized to no prophylaxis or to oral cryotherapy (swishing with ice chips for 30 minutes immediately following administration of chemotherapy). Local vasoconstriction should reduce blood flow to the oral mucosa and therefore diminish fluorouracil distribution to the oral mucosa, resulting in reduced mucositis. Assessments of mucositis by both patient and physician at two to four weeks following treatment demonstrated a significant difference in mean mucositis grade. A follow-up parallel study[33] compared 30-minute vs 60-minute cryotherapy for the same patient population and found no additional benefit to prolonging the treatment.
Soft-Laser Therapy

A retrospective study[34] reviewed the use of low-intensity laser irradiation for treatment and prophylaxis of mucositis in patients who receive fluorouracil-based chemotherapy and who have a history of stomatotoxicity with this regimen. This modality was examined due to reports of improved wound healing and accelerated replication of myofibroblasts after laser therapy. Three groups were identified: 20 control patients, 16 laser treatment patients, and 23 laser prophylaxis patients. The laser treatment patients healed from grade 4 mucositis in an average of 8.1 days compared with 19.3 days in the control group. In the prevention group, mucositis occurred in only 7% of chemotherapy cycles compared with 43% in the control group.

Table 2. Effective Preventive Interventions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Regimen</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Leucovorin</td>
<td>Varies on dosage and/or levels of methotrexate</td>
<td>Effective rescue for high-dose methotrexate</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>10-15 mL rinse 2 to 3 times daily</td>
<td>More effective with chemotherapy vs radiation induced mucositis</td>
</tr>
<tr>
<td>Nystatin</td>
<td>5-10 mL swish/expectorate every 4 to 6 hours</td>
<td>Less effective than clortrimazole, fluconazole</td>
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<tr>
<td>Clotrimazole</td>
<td>10-mg troche dissolved in mouth 5 times daily</td>
<td>Prevention of oral thrush</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>100-400 mg by mouth daily</td>
<td>Higher doses to prevent systemic Candida infections</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>250 mg/m2 intravenously every 8 hours on day -3 through day +12 BMT patients</td>
<td>Effective in HSV seropositive</td>
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<tr>
<td>Sucralfate</td>
<td>1 gram swish/swallow 4 times per day</td>
<td>Modest benefit</td>
</tr>
<tr>
<td>Oral cryotherapy</td>
<td>34, 35 Ice chip swish every 30 minutes</td>
<td>With bolus 5-fluorouracil</td>
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HSV = herpes simplex virus
BMT = bone marrow transplantation

Conclusions

The search for active agents for the prophylaxis of chemotherapy-induced mucositis has been frustrating, with no single agent demonstrating dramatic results in all settings. Careful evaluation of the literature is necessary to determine the relative merit of these agents and techniques (Tables 2, 3, and 4). Interventions often produce impressive results in noncomparative studies but fail to uphold the expectations in the face of a controlled clinical trial. The subjective endpoints for assessing mucositis are susceptible to a high risk of evaluator bias in most studies. Frequently, control groups have not contained placebo due to concern about exacerbating mucositis with additional oral medications; however, without placebo control, the bias that plagues many of these studies will not be eliminated. With attention to these design issues, future researchers may be successful in eliminating false leads and discovering agents with the capacity to truly impact on the quality of life of patients receiving cancer chemotherapy.

In the current clinical climate, in which reliably effective prophylaxis against chemotherapy-induced mucositis remains a goal rather than a reality, research also is underway to improve the treatment of this complication. An Eastern Cooperative Oncology Group protocol (E1Z93), Phase III Study of Treatment of Chemotherapy Associated Mucositis: Sucralfate Suspension Versus Vitamin E is active and enrolling patients. This randomized, open-label trial will compare the efficacy of swishing and swallowing 1 g of sucralfate four times daily and vitamin E applied topically twice daily in patients with grade 2 or greater stomatitis following chemotherapy. The results of this trial will help to direct supportive therapy in these patients.

Appreciation is expressed to John Horton, MB, ChB, for editorial guidance.

Table 3. Ineffective Preventive Interventions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Regimen</th>
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<tr>
<td>Prostaglandin E2 (PGE2)</td>
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<tr>
<td>Allopurinol</td>
<td>20, 21</td>
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<tr>
<td>Pentoxifylline (PTX)</td>
<td>26, 29</td>
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<tr>
<td>Filgrastim</td>
<td>31, 32</td>
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In the current clinical climate, in which reliably effective prophylaxis against chemotherapy-induced mucositis remains a goal rather than a reality, research also is underway to improve the treatment of this complication. An Eastern Cooperative Oncology Group protocol (E1Z93, Phase III Study of Treatment for Chemotherapy-Associated Mucositis: Sucralfate Suspension Versus Vitamin E) is active and enrolling patients. This randomized, open-label trial will compare the efficacy of swishing and swallowing 1 g of sucralfate four times daily and vitamin E applied topically twice daily in patients with grade 2 or greater stomatitis following chemotherapy. The results of this trial will help to direct supportive therapy in these patients.

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Table 4. Interventions Worthy of Further Study

<table>
<thead>
<tr>
<th>Agent</th>
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<tr>
<td>Beta-carotene</td>
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<td>Propantheline</td>
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<tr>
<td>Leucovorin for allogeneic BMT (PTX)</td>
<td>24</td>
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<tr>
<td>Lisofylline (CT1501R)</td>
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</tr>
<tr>
<td>Soft-laser therapy</td>
<td>35</td>
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References


