ORAL AND GASTROINTESTINAL MUCOSITIS: NOVEL INSIGHTS INTO PATHOPHYSIOLOGY AND POTENTIAL THERAPIES

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ABSTRACT

Mucositis is a dose-limiting side effect of high-dose chemotherapy and radiotherapy currently used in many cancer treatments and in the intensive conditioning that precedes hematopoietic stem cell transplantation (HSCT). Increasing awareness of the clinical and economic consequences of mucositis and ongoing research into the molecular and cellular mechanisms of mucositis have spurred development of novel strategies for the prevention or treatment of this debilitating disorder. In particular, the elucidation of 5 phases of mucositis pathophysiology—initiation, up-regulation and message generation, signaling, ulceration, and healing—has provided a road map for the development of several novel biologicals. After a summary of mucositis epidemiology and assessment methods, this article reviews the mechanism, administration, phase of drug development, and preliminary clinical data of several novel antimucositis agents, including palifermin (now approved), Aesgen-14 (L-glutamine in proprietary drug delivery system), low-energy laser therapy, benzydamine hydrochloride, and amifostine. It is likely that 1 or more new agents will emerge as a standard for preventing or treating mucositis in the next 1 to 5 years. Eventually, combination regimens will likely become available to reduce mucositis to a level at which high-dose chemotherapy and HSCT can achieve maximum anticancer outcomes. (*Adv Stud Med.* 2005;5(4B):S299-S310)

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The scope of research related to oral and gastrointestinal (GI) mucositis secondary to high-dose chemotherapy has strategically expanded in recent years.[1-4] Collectively, researchers have addressed several fundamental molecular mechanisms related to causation and potential novel therapies, in addition to previously unexamined aspects of mucositis related to epidemiology, clinical complications, objective assessments of mucosal injury, and economic impact.[4,5]

The current state of science is such that 1 or more of today's mucositis investigational drugs will likely become available for clinical use within 1 to 5 years. This would represent a strategically important new opportunity in oncology practice. Until now, clinicians have dealt with chemotherapy-associated and radiation-associated mucositis through alteration in cancer therapy protocols (eg, using alternative regimens or reduced doses of radiation or chemotherapy) or by palliation with various techniques and agents for which use has been dictated more by empiricism than evidence.[4] In coming years, if clinicians are instead able to administer therapies directed to molecular targets associated with mucosal injury, then improved efficacy is likely and better overall outcomes will follow.

To reduce tissue injury and to enhance proliferative repair in this context of chemotherapy-induced epithelial cell damage, a variety of cytokines and growth factors have been tested, preclinically or clinically, including agents such as keratinocyte growth factor (KGF), interleukin (IL)-11, transforming growth factor beta, granulocyte macrophage colony-stimulating factor (GM-CSF), and RK-0202 (N-acetyl-L-cysteine) in thermosetting. Research aimed at identifying other new agents continues.[6]

To help clinicians prepare for an era of more targeted mucositis therapy, this article will review several novel mucositis therapies in various stages of clinical

testing. To set the stage for this review, the pathophysiology of chemotherapy-induced mucositis will be described and the translational link between the laboratory and clinical setting will be emphasized. The discussion will be framed in the context of the contemporary model for mucositis involving the alimentary tract. Specific issues with relevance to patients undergoing hematopoietic stem cell transplantation (HSCT) will be highlighted.

Scope of the Problem

Until recently, the reporting of mucositis in cancer clinical trials was a secondary research objective and, thus, information on incidence and risk factors was typically incomplete. However, assessment of the more recent literature now identifies 3 cancer therapy patient cohorts in whom the incidence of clinically significant oral mucositis is highest: myelosuppressive chemotherapy for solid tumors; radiation for head and neck cancers; and myeloablative conditioning regimens for HSCT.

The relationship of cytotoxic cancer therapy to oral mucositis was recently summarized in an evidence-based review by Sonis et al.[3] Although patient-related mucositis risk factors such as poor oral health, age, and history of previous cancer treatment are suspected,[7] these are less documented than treatment-related risk factors. In the hundreds of studies evaluated in the review by Sonis et al, incidence of mucositis varied significantly by regimen and modality.[3] For example, anthracycline-based regimens were most often associated with rates of grade 3 oral mucositis in the 1% to 10% range, except when they were combined with 5-fluorouracil (5-FU). Rates of grade 3 mucositis with taxane-based and platinum-based regimens were also generally below 10%, except when combined with 5-FU or radiation. Rates of severe oral mucositis were especially high in patients with GI malignancies (53%; 95% confidence interval [CI], 40%–44%; in 4 studies), a group that often

receives therapy based on 5-FU, CPT-11, and radiation. In addition, nearly 50% of all patients with head and neck or esophageal cancer developed a World Health Organization (WHO) grade 3 or higher oral mucositis in the primary portal. Overall, in the general population of patients with cancer, the highest rates of oral mucositis seem to be associated with treatment-related factors, including radiation delivered to the head and neck, high-dose chemotherapy, combined chemotherapy and radiation, and chemotherapy with 5-FU, methotrexate, and etoposide.[7]

Some of the highest rates of a WHO grade 3 or higher oral mucositis have been observed in patients who underwent HSCT (Table 1).[3] In adults, the HSCT rates are generally in the 30% to 50% range with high-dose chemoablative regimens, but they can exceed 60% when combined with total body irradiation (TBI). The role of conditioning regimen intensity in determining mucositis risk is generally acknowledged. In particular, regimens using melphalan or TBI are associated with profound oral mucositis in HSCT recipients.[4]

Some researchers are of the view that recipients of allogeneic bone marrow transplant (BMT) experience higher rates of mucositis than patients receiving autol-

Table 1. Relation Between BMT/HSCT Conditioning Regimen and Risk of Grade 3/4 Oral Mucositis and Gastrointestinal Mucositis

Conditioning Regimen	Studies	Patients, n	Risk of Grade 3/4 Oral Mucositis		Risk of Grade 3/4 GI Mucositis	
			%	95% CI	%	95% CI
Adult BMT						
With TBI	8	611	64	61–68	7	3–16
Busulfan (no TBI)	10	360	52	47–55	10	7–14
Other (no TBI)	3	439	31	27–35	15	11–19
Stem cells: myeloma	5	139	36	30–43	14	8–23
Stem cells: solid tumor	9	266	27	24–31	6	4–9
Pediatric BMT						
With TBI	7	320	42	37–47	33	12-62
With busulfan/etoposide/ cyclophosphamide (no TBI)	3	36	27	13–42	NR	NR
With melphalan/carboplatin/ etoposide (no TBI)	4	59	31	25–40	14	3–36

BMT = bone marrow transplantation; CI = confidence interval; HSCT = hematopoietic stem cell transplantation; TBI = total body irradiation.
Adapted from Sonis et al. *Cancer.* 2004;100(suppl 9):1995-2025.[3]

ogous BMT caused not only by differences in the typical conditioning regimen but also by the need for an agent, such as methotrexate, to prevent graft-versus-host disease.[7] However, as outlined in the clinician interview with Dr Spielberger in this issue of **Advanced Studies *in* Medicine**, many of the intensive chemoradiotherapy conditioning regimens now commonly used in modern autologous transplantation settings are virtually certain to produce severe mucositis. Clearly, the impact of reduced-intensity conditioning regimens on oral and GI mucositis in patients receiving HSCT warrants further study. However, at present, the HSCT clinical team must be prepared to deal with mucositis and its sequelae by educating the patient and caregivers, monitoring the patient's status including oral mucosal examinations, and instituting supportive care measures as clinically indicated.

The clinical and economic impact of oral mucositis on patients undergoing autologous and allogeneic HSCT was addressed specifically in a seminal study by Sonis et al.[8] In this study, 92 patients undergoing transplantation were evaluated for severity of oral mucositis by using the Oral Mucositis Assessment Scale (OMAS), which measures location and severity of oral ulceration/pseudomembrane. Erythema also was measured by using a 5-point scale of 0 (normal) to 5 (most severe). A 1-point increase in peak OMAS scores was associated with the following:

- 1.0 additional day with fever ($P < .01$)
- 2.1-fold increase in risk of significant infection ($P < .01$)
- 2.7 additional days of total parenteral nutrition ($P < .0001$)
- 2.6 additional days of injectable narcotic therapy ($P < .0001$)
- 2.6 additional hospital days ($P < .01$)
- \$25 405 in additional hospital charges ($P < .0001$)
- 3.9-fold increase in 100-day mortality risk ($P < .01$).

Overall, the hospital charges averaged \$42 749 more for patients undergoing HSCT who had mucosal ulcerations, as compared with those patients without the lesions ($P = .06$).

Similarly, an analysis by Elting et al in a non-HSCT population of patients with cancer found that chemotherapy-induced grade 3/4 mucositis led to additional medical-related costs of approximately \$5565 per cycle.[9] In this retrospective analysis of 599 patients undergoing 1236 cycles of myelosuppressive chemotherapy for solid tumors, infection complicated by mucositis (especially GI mucositis) occurred during 73% of the cycles; without mucositis, only during 36% of the cycles ($P < .0001$). The high incidence of mucositis-associated serious toxicity resulted in a doubling of the average number of hospital days per cycle (7.7 days vs 3.9 days; $P < .0001$).

These data demonstrate the potential clinical and economic impact of oral and GI mucositis on patients with cancer who are receiving myelosuppressive chemotherapy, particularly patients undergoing HSCT who receive the most intensive form of conditioning as part of their planned regimen. Indeed, it has been these and other recent studies of the epidemiology, clinical complications, and health resource utilization of chemotherapy-associated mucositis that have helped to define the long-standing gaps and inconsistencies in our current treatment approaches and, within the past 5 years, have shaped the imperative to find novel therapies for this highly debilitating condition.

As the search for more rational and targeted mucositis therapies began, pathophysiologic studies and related molecular and cellular investigations quickly revealed that a continuum of alimentary tract mucosal injury occurs in many patients with cancer. The precise nature of this continuum of mucosal injury and the underlying mechanistic interactions between damaged oral and GI mucosa are still under active investigation in several laboratories. The knowledge derived from this ongoing basic research will inform the clinical research and oncology community about new strategies for more comprehensive preventive and therapeutic interventions in the future. In the meantime, a contemporary pathobiologic model has emerged in the past 5 years that provides a rational basis for drug development.

CONTEMPORARY PATHOBIOLOGIC MODEL

Until recently, oral mucositis has been viewed principally as a simple and relatively direct epithelial phenomenon. Although the oral epithelium is obviously a key site for injury, a variety of compelling preclinical and clinical studies now make clear that oral mucositis is a "transtissue" toxicity, with the submucosa exerting primary and secondary influences on damaged and healing oral epithelium.[10-18] This cross-talk among diverse tissues and cell types is initiated within hours of the first admin-

istration of mucotoxic chemotherapy or radiation therapy and is characterized by a multifaceted inflammatory cascade with strong genetic influences.

Although the current model is still evolving, it has been defined eloquently by Sonis et al as having 5 principal phases: initiation, up-regulation and message generation, amplification and signaling, ulceration, and healing.[3,18]

INITIATION

The initial injury (initiation) begins within hours of administration of the first dose of chemotherapy or radiation. The entire mucosal surface is at risk, and the early changes are typified by generation of reactive oxygen species. These free radicals promote a cascade of injurious molecular events. The injury can extend to replicating cells and can cause direct damage to DNA.

UP-REGULATION AND MESSAGE GENERATION

The second phase (up-regulation and message generating phase) is characterized by activation of transcription factors (eg, nuclear factor kappa B [NF-κB]) with subsequent up-regulation of various genes and related proteins. Of central importance in mucositis is the increased production of the proinflammatory cytokines tumor necrosis factor (TNF)-α and IL-1 β, both of which target and cause direct tissue injury and apoptosis of surrounding cells. As with the initial events described above, both the epithelium and connective tissue can be affected adversely. As the injury accumulates, the oral mucosa can become symptomatic (sensation of burning and pain) and erythematous.

AMPLIFICATION AND SIGNALING

Positive feedback loops are generated in the third phase (amplification and signaling). In some cases, the same cytokine that targeted tissues for direct damage will also further stimulate genes responsible for cytokine production. For example, cytokines such as TNF-α can upregulate or amplify the transcription factor NF-κB or activate the enzymes responsible for activating the ceramide pathway that also leads to apoptosis. These feedback loops sustain and escalate the severity of mucosal injury even after the instigating cytotoxic cancer therapy has been discontinued.

ULCERATION

The first 3 phases eventuate in the fourth phase (ulceration), which has commonly been viewed as the classic expression of mucositis. In this phase, the mucosa is obviously and visibly disrupted, underlying neural injury leading to pain occurs, and bacterial colonization of the lesions is possible. As such, the ulceration phase is principally responsible for most of the clinical and economic consequences described earlier in this article. In patients with neutropenia, the risk of systemic infection originating in these lesions is also substantially increased. In addition, metabolic products of bacterial cell walls can further stimulate macrophage-directed inflammatory responses.

HEALING

The fifth phase (healing) occurs in the 2 to 4 weeks after discontinuation of the cancer treatment, and the inflammatory component and its sequelae gradually resolve. This tissue recovery is not passive but is governed actively by regulatory proteins expressed by the extracellular matrix. These molecules promote the migration, proliferation, and maturation of new mucosal epithelium. Eventually, the wound is epithelialized and the submucosa re-establishes its function and architecture. Symptoms gradually resolve as this healing ensues.

Each of these phases can be considered as a conceptual target for novel prevention or treatment interventions. However, the clinician should be aware that this classification system, despite its high value in modeling the incredibly complex process of wound healing, is nonetheless artificial in its sequential time line. Based on current knowledge of inflammation biology and other mucosal disease (eg, inflammatory bowel disease) or toxicity (eg, nausea and emesis),[5] considerably more overlap and integration of the mechanisms of injury and healing is more likely to occur than is currently known. For the clinician, this still unresolved complexity of interactions suggest the unlikelihood that any single drug intervention will fully mitigate the expression of clinically significant oral mucositis. Thus, once single-agent approaches become available to clinicians for mucositis management, the next step will undoubtedly be the testing of combination therapies that may have additive or synergistic benefit to the patient.

Pathobiologic modeling of mucositis continues to be an evolving body of knowledge with dynamic implications for drug development. As a variety of new mechanism-based mucositis therapies continue to be developed, clinicians should remain aware of advances

in other areas of related research such as novel approaches to drug delivery and, as discussed later in this article, improved methods to assess alimentary mucositis.

NOVEL THERAPIES

Conceptual modeling of mucositis has provided the intellectual road map for the development of more effective antimucositis agents. The need to test these new agents has, in turn, spurred improvements in the clinical monitoring tools used to help each patient. These tools help clinicians to assess patient symptoms, signs, and functional disturbances secondary to the mucosal toxicity. For example, Schubert et al identified the importance of delineating specific degrees of mucosal tissue injury, distinct from patient symptoms and/or functional compromise.[19] Although the OMAS described earlier in this article is founded mainly on visual measures of ulceration and erythema, results from this scale can also be correlated with pain reports of patients and more global scales such as those developed by WHO. This evolving approach has allowed investigators to evaluate study drug intervention relative to tissue response and patient experience. Each of these tools can be considered while the clinical trial endpoints are being defined. For example, it may be principally useful to assess degree of tissue inflammation in phase II studies, while using WHO-based assessments of symptoms, signs, and functional disturbances in phase III studies.

Despite the continuing advances in measuring the location and severity of oral mucositis, oncologists still need improved assessment scales to measure the severity and location of GI mucositis in patients receiving chemotherapy or radiation. Presently, because of the difficulty of visual inspection of the alimentary tract distal to the oropharynx in these patients, the outcomes of nausea, vomiting, and diarrhea are used as prime clinical surrogates for the assessment and management of GI mucositis. Although they are important in a clinical setting, these measures do not serve as precise indicators of the morphologic and functional disturbances expected to occur over the typical course of GI injury and repair seen after HSCT. Also, the development of agents to combat GI mucositis, until recently, suffered from the lack of an appropriate animal model in which the desired anticancer effects of the conditioning regimen were not diminished.[20-22]

A new animal model has emerged, using the female rat with implanted spontaneous isogenic breast adeno-carcinoma. As new mucositis therapies are introduced in coming years, these inherent difficulties of experimentally screening and then clinically assessing GI mucositis should be recalled. An agent that works well in oral mucositis should not be presumed to be effective in GI mucositis, or vice versa. Although many of the molecular mechanisms of mucosal injury outlined in the previous section can be assumed to apply, in a general sense, to oral and GI mucosa, there are key differences in cell structure and kinetics between the upper and lower GI tract.[23]

The US Food and Drug Administration (FDA) has approved palifermin for the prevention or treatment of oral mucositis in patients undergoing HSCT. The following section describes palifermin, and select agents currently in development, based on data in the public domain; the emphasis is on agents intended to block or modify any steps in the complex cellular and molecular pathways of mucositic pathophysiology, as described earlier in this article. Agents directed to symptom or infection management (eg, pain medications or antimicrobials, respectively) are not reviewed, even though they represent important intervention strategies in current oncology practice. Nonpharmacologic treatment strategies not discussed here include intensity-modulated radiation therapy, lead-based shielding of healthy tissue to reduce radiation-induced oral mucositis, and reduced-intensity conditioning regimens in select patients. In the future, a combination of strategies involving targeted therapy, palliative care, and harm reduction will be required to reduce the impact of mucositis, thus maximizing the safety and efficacy of potentially life-saving stem cell transplantation procedures.

KGF-1 AND KGF-2

Over the past decade, researchers have documented the many biological effects of KGF on epithelial cells, including enhanced cellular proliferation, cellular migration, and cellular morphogenesis.[24] Unlike many other fibroblast growth factors, KGF seems to target epithelial cells specifically.[25] Based on these actions, KGF has been studied for its potential as a GI antimucotoxic. This line of preclinical research revealed that KGF promoted healing in many regions of the GI tract, including the gastric mucosa[26] and small intestinal mucosa.[27-29] Most of these animal studies showed that KGF seemed to be more effective in reducing mucositis

when administered before chemotherapy or radiotherapy rather than after treatment,[27] perhaps by acting as a gut growth primer.[20] Based on the promising preclinical data,[28] KGF clinical trials commenced several years ago.

KGF-1 (palifermin) and KGF-2 (repifermin) are similar, although not homologous, proteins.[30,31] Both stimulate the growth of basal epithelial cells and have been considered as appropriate candidates for boosting the epithelial thickening and the wound healing phases of mucositis. Based on these 2 distinct target phases, 2 separate clinical uses and actions for KGF have been proposed: prophylactic administration to enhance the thickness of the epithelial barrier before direct injury by cancer therapy and administration during the ulcerative phase to enhance tissue repair. This hypothesis has led to trials calling for the administration of KGF before the conditioning regimen and again after the autologous HSCT. Animal data suggest that recombinant KGF may also be used in the transplantation setting for reducing the severity of graft-versus-host disease while preserving the graft-versus-leukemia effect.[32] These relationships are intriguing because acute oral graft-versus-host disease can, in some patients, mimic oral mucositis caused by chemotherapy.

Repifermin was used in phase II trials until early 2004 when the manufacturer halted all studies because of the agent's failure to meet its primary endpoint (reduction of grade 2–4 mucositis by 40% vs placebo).[33] In this trial involving 92 patients receiving 2 autologous HSCTs for multiple myeloma, the manufacturer stated that repifermin was well tolerated across all doses with a safety profile similar to that of a placebo. This key trial with repifermin had been initiated based on preliminary data from a smaller trial (*n* = 42), showing that the recombinant KGF-2 significantly reduced the incidence of grade 2 to 4 oral mucositis in patients receiving various conditioning regimens before undergoing autologous HSCT (*P* <.0069).[4,34] In patients receiving the higher dose (50 μg/kg) of repifermin, the incidence of grade 2 to 4 mucositis (7/14) was reduced by 50%, as compared with the control group.

The clinical database on palifermin is more advanced, and the manufacturer has received approval from the FDA based on phase III results originally presented in abstract form[35,36]

and now published in *The New England Journal of Medicine*.[37] The pivotal double-blind phase III study focused on 212 patients with hematologic malignancies who were undergoing autologous HSCT with intensive conditioning that included high-dose chemotherapy (60 mg/kg etoposide and 100 mg/kg cyclophosphamide) with TBI (12 Gy). The palifermin was administered for 3 consecutive days before TBI and again for 3 days after the transplant.

As shown in Table 2, palifermin reduced the incidence and duration of severe oral mucositis and medical resource use.[36] Overall, patients who received palifermin suffered significantly fewer days with severe ulcerative oral mucositis (grades 3/4), as compared to those patients receiving a placebo (*P* <.001). In addition, palifermin helped to protect patients from the most severe form of oral mucositis (20% of palifermin-treated patients experienced grade 4 mucositis vs 62% of placebo-treated patients; *P* <.001). Patient-related outcomes as determined with daily measurements of mouth and throat soreness also improved significantly in the group receiving palifermin (0.7 vs 1.3; *P* = .0001). Palifermin also produced a 40% or greater reduction versus a placebo in patient-reported limitations related to eating, talking, sleeping, swallowing, and drinking (*P* <.001). Adverse events seen more frequently in the patients treated with palifermin included mild skin and oral erythema with or without edema and asymptomatic transient increases in serum amylase and lipase.

Table 2. Palifermin for Oral Mucositis in Autologous HSCT

Result	Placebo (*n* = 106)	Palifermin (*n* = 106)	*P* value
Patients w/ mucositis WHO grade 3/4, %	98	63	<.001
Patients w/ mucositis WHO grade 4, %	62	20	<.001
Mean (SD) days w/ mucositis WHO grade 3/4	10.4 (6.2)	3.7 (4.1)	<.001
Mean (SD) days of inpatient hospitalization	17.3 (5.38)	15.3 (5.06)	.008
Mean (SD) days analgesic opioid use	11.8 (5.7)	6.8 (5.7)	.0001
Patients w/ mucositis-related parenteral feeding, %	43	11	<.001

HSCT = hematopoietic stem cell transplantation; WHO = World Health Organization.
Adapted from Bensinger et al. *Biol Blood Marrow Transplant*. 2004;10(suppl):31.[36]

CRYOTHERAPY

In cryotherapy, ice chips are dissolved in the oral cavity for 5 minutes before and 25 minutes after bolus (not continuous) administration of 5-FU. The intent is to minimize cytotoxicity on the mucosa by decreasing circulation at peak blood levels. Cryotherapy protects proliferating cell layers via vasoconstriction and may prevent later damage secondary to chemotherapy. Because ice is inexpensive and readily available, cryotherapy, which caries a low risk for adverse effects, is used in many clinical centers. Does it work? Ice chips have been tested in several clinical trials to test their effectiveness in reducing the degree of mucositis in chemotherapy, mostly involving patients receiving bolus 5-FU.[38-40] The consensus of opinion, as summarized in the Cochrane Review and the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) guidelines, is that cryotherapy does seem to be effective in preventing oral mucositis in patients receiving 5-FU.[4,41] However, because not many patients undergoing HSCT receive 5-FU as part of their conditioning, there is continuing interest in using this approach with other agents. A few small trials have evaluated cryotherapy with melphalan,[42,43] but additional randomized clinical trials are warranted before the technique is applied broadly to patients undergoing HSCT who are receiving high-intensity conditioning.

L-GLUTAMINE WITH A NOVEL DRUG DELIVERY TECHNOLOGY

L-glutamine is a conditionally essential amino acid that is the main source of fuel for respiration in the intestinal epithelial cells and other rapidly dividing cells, including lymphocytes and macrophages.[44] Glutamine is also critical in nitrogen transfer between tissues and for the regulation of protein synthesis. Preclinical testing of glutamine showed a protective effect against intestinal damage after radiation.[45,46] In addition to this apparent mucosal protective effect, glutamine was also shown in an animal model to be a potential enhancer of chemotherapy.[47] However, despite these positive early findings, tests of glutamine in a phase III placebo-controlled trial involving patients receiving 5-FU failed to show any protective benefit.[48]

The failure of oral glutamine to produce clinical benefits in these early trials was thought to be a result of the unmodified agent's poor solubility, limited cell uptake, and overall chemical liability. A novel drug delivery system was developed to concentrate active glutamine near the epithelial cells in the at-risk oral mucosa. The vehicle for this system known as Aesgen-14 (AES-14) consists of ingredients classified by the FDA as "generally regarded as safe." The product is used 2 to 3 times per day as a mouth rinse and, based on in vitro studies, is designed to increase delivery and bioactivity of active glutamine to target mucosa by 10-fold to 100-fold. Phase III clinical trials using AES-14 now have been completed, involving 326 women who developed WHO grade 2 to 4 mucositis in the first screening cycle of the 3 planned cycles of anthracycline-based chemotherapy. In this randomized, double-blind, crossover trial, the incidence of grade 2 to 4 mucositis in the first treatment cycle was 22% less with AES-14 versus a placebo (P = .0261); analysis of the crossover data indicated that this mucoprotective effect appeared to carry over into subsequent treatment cycles.[49] The safety profile was comparable to that of a placebo.

AMIFOSTINE

Amifostine is a free radical scavenger that is available in the United States to protect against radiation-induced salivary gland injury. Based on this antioxidant's ability to accumulate in epithelial tissues and to reduce the incidence of moderate-to-severe xerostomia after radiotherapy for head and neck cancer, researchers have begun testing the hypothesis that amifostine can also reduce mucositis in the chemoradiation setting by selectively protecting nonmalignant cells from the effects of radiation therapy without providing any detectable protection of malignant cells.[50] Amifostine is usually delivered subcutaneously or intravenously.[51]

Several studies have documented the efficacy of this organic thiophosphate in reducing the incidence and severity of xerostomia when used prophylactically in patients receiving radiotherapy that includes the oral mucosa in the treatment field. Most of this research has been conducted involving patients with head and neck cancers[52,53]; to date, there has been limited evidence of mucositis efficacy in these patients. For example, in a phase III randomized trial of amifostine involving 315 patients receiving radiation for squamous cell cancer of the head and neck, the radioprotectant reduced xerostomia but did not reduce mucositis. Grade 3 or higher mucositis occurred in 35% of the group receiving amifostine and in 39% of

the group receiving only radiotherapy (P = .48).[52] In addition, amifostine's success in reducing mucositis has also been limited in studies of patients receiving high-dose 5-FU[54] or in patients receiving stem cell transplantation with TBI.[55] A recent Cochrane Review and the latest American Society of Clinical Oncology guidelines both conclude that amifostine provides minimal benefit in preventing mucositis in patients with cancer.[41,56] The new MASCC/ISOO guidelines give the agent a "C" recommendation (indicative of inconsistent findings) for reducing esophagitis in patients with non-small cell lung cancer.[4] The major current areas of amifostine use seem to be in the reduction of esophagitis in radiotherapy for non-small cell lung cancer[57-59] and, perhaps, in radiation proctitis.[60-62] Most recently, there have been reports that amifostine reduces the incidence of severe mucositis (33% vs 65%; P <.05) caused by high-dose melphalan in patients receiving stem cell transplantation.[63] Results from several other recent reports of amifostine use with myeloablative conditioning regimens have been mixed.[64-67]

As testing of amifostine continues, several issues must be resolved. The optimal mucoprotective dose, schedule, and administration form have yet to be determined. The drug is tolerated poorly by patients when it is administered in high doses or via the current FDA-approved intravenous fashion; the acute toxicities include nausea, emesis, hypotension, allergic reactions, and taste disturbances.[4] Finally, and perhaps most significantly, there are lingering concerns with radioprotectors, such as amifostine, regarding the potential hazard of collateral tumor protection, a concern that can be ruled out only by large and long-term clinical studies.[50]

GM-CSF AND G-CSF

Granulocyte macrophage colony-stimulating factor and granulocyte colony-stimulating factor (G-CSF) may retard the breakdown of normal epithelium.[68] These cytokines may also enhance mucosal defenses in the mouth via accumulation of activated neutrophils and, independently, stimulation of wound healing. Based on these actions, GM-CSF and G-CSF have now been tested, topically and systemically, for oral mucositis in chemotherapy settings.

The results from the many studies evaluating GM-CSF and G-CSF for preventing mucositis (or reducing related pain) are inconsistent across various populations.[53,69] Many of the published studies have been open and nonrandomized. Nonetheless, the Cochrane Review concluded that GM-CSF was capable of preventing mucositis in patients receiving chemotherapy (relative risk = 0.51; 95% CI, 0.29–0.91).[41] Still, a recent randomized and double-blind trial found that prophylaxis with GM-CSF mouthwash did not reduce the severity of mucositis developing in patients undergoing autologous HSCT.[70] To confuse matters further, a separate Cochrane Review of mucositis treatments found that GM-CSF decreased the time to healing by 3.5 days (95% CI, -4.1 to -2.9) versus povidone iodine.[71] The use of these growth factors for mucositis prevention or treatment remains investigational, and the systemic use of GM-CSF is associated with potentially significant side effects, including local skin reaction, fever, bone pain, and nausea.

TRANSFORMING GROWTH FACTOR β

Transforming growth factor β (TGF-β_3) plays a central role in cell proliferation[72] and has now joined the lengthening list of growth factors being tested for their antimucotoxic potential.[73,74] This cytokine causes reversible arrest of cells in G_1. This induction of a resting phase is a mechanism with obvious potential for protecting active-cycling epithelial cells during periods of vulnerability because of high-dose cancer therapy. The strategy with TGF-β_3 is to administer the drug before chemotherapy.

The efficacy of TGF-β_3 in reducing severity of cancer therapy-induced oral mucositis has been studied in a limited number of clinical trials. A phase I study of TGF-β_3 mouthwash used by 11 patients with breast cancer demonstrated safety and possible efficacy,[75] but interim results from 2 double-blind placebo-controlled studies failed to demonstrate efficacy involving patients with lymphomas or solid tumors who were receiving high-dose chemotherapy.[76] The study involving patients with solid tumors was halted prematurely because of evidence from other trials that indicated the formulation, dose, and regimen were likely suboptimal. Therefore, based on research to date, additional investigation is required to determine if TGF-β_3 will be an effective future treatment for mucositis.

LASER (LOW-ENERGY LIGHT DIODE)

Low-level laser therapy (LLLT) is still not widely available in cancer treatment centers because of the high cost of equipment and the need for trained technologists. However, the recent guidelines issued by

MASCC/ISOO recommend the use of LLLT (grade B evidence) to reduce the incidence of mucositis and associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT.[4] The precise LLLT mechanism of biostimulation is unclear, but the intervention may promote wound healing.

Clinical trials involving LLLT suggest some efficacy with the low-energy helium-neon laser in reducing the severity of oral mucositis in patients receiving high-dose chemotherapy followed by bone marrow transplantation.[77,78] The technology is commercially available, although cost of the equipment and training requirements are limiting factors in practical uptake and use. Additional research is needed to test various dosing schema and different wavelengths with diode lasers.

BENZYDAMINE HYDROCHLORIDE

Benzydamine hydrochloride is a unique topical nonsteroidal anti-inflammatory agent. In addition to its anti-inflammatory properties, the agent also displays histoprotective and analgesic or anesthetic effects that appear to be cumulative and prolonged. The primary mechanism of action may involve inhibition of pro-inflammatory cytokines, such as TNF-α. Benzydamine hydrochloride oral rinse is widely available in Canada and Europe, but it is not commercially available in the United States. Unfortunately, the pharmaceutical manufacturer has cancelled its mucositis drug development program.

Several small placebo-controlled trials provided the initial evidence that benzydamine hydrochloride alleviates pain and reduces the incidence and severity of oral mucositis caused by chemotherapy or radiotherapy.[53] A recent large, randomized, double-blind clinical trial appears to support the use of benzydamine hydrochloride oral rinse prophylactically in patients receiving conventional doses of radiation therapy to the head and neck.[79] However, a recent Cochrane Review of treatments for chemotherapy-associated mucositis found that benzydamine hydrochloride was not effective in treating ulcerations or related pain.[71]

BIOADHERENT ORAL GEL

Gelclair (OSI Pharmaceuticals, Inc, Melville, NY) is the trade name for a concentrated, bioadherent oral gel that has been FDA approved as a class I medical device indicated for relief and management of oral pain associated with mucositis caused by chemotherapy or radiation therapy, oral surgery, or other ulcer-causing traumas or diseases.[80,81] The key ingredients of Gelclair are sodium hyaluronate, polyvinylpyrrolidone, and glycyrrhetinic acid. The prescription gel likely exerts pain relief by forming an adherent barrier over the oral mucosa, shielding the exposed or sensitized nerves. The product is administered 3 times a day, dissolved in 1 or 2 tablespoons of water, stirred, and then used to rinse the mouth (including gargling) for at least 1 minute before being expectorated.

Clinical data on Gelclair are limited to open-label trials involving 30 patients with mucositis or mouth ulcers from diverse causes.[80,82] Significant decreases in oral pain were reported in these preliminary studies, but there is limited evidence related to degree of mucositis. Controlled studies in patients with cancer are warranted.

INTERLEUKIN-11

For more than a decade, IL-11 has been discussed as a potential treatment for mucositis. In the early 1990s, researchers showed that IL-11 increased rodent survival and increased cellular proliferation in the intestine while reducing apoptosis after high-dose chemotherapy.[83-85] Later animal studies demonstrated that IL-11 reduced damage from radiotherapy[14,86] and chemotherapy.[21,87] The mechanisms underlying these potentially useful actions remain unknown for clinical use. Defining these mechanisms of action and confirming preliminary evidence that IL-11 does not interfere with chemotherapy or cause tumor growth[21,87] are priorities for researchers in advance of any extensive clinical program.

CONCLUSIONS

The past 5 years have produced strategically important advances in research related to mucositis in patients with cancer. These discoveries have occurred simultaneously at many different levels, including pathobiology, mucosal assessment scales, drug delivery, and epidemiology relative to clinical and economic impact. This newly expanded foundation may lead to the approval of new, more biologically targeted agents for oral and GI mucositis, thus leading to significant reductions in morbidity in those patients with cancer who are at highest risk, including those patients undergoing HSCT. The FDA approval of palifermin (KGF-1) ushers in this new era. This new agent may also permit implementation of more intensive cancer therapy or conditioning regimens than currently are

feasible because of dose-limiting mucosal toxicity. Because of the biological complexity and overlapping molecular pathways that seem to drive mucositis, multiple mucoprotective drugs may eventually be used in these high-risk patients to address multiple phases of the mucositis pathophysiologic course.

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