Updated Clinical Practice Guidelines for the Prevention and Treatment of Mucositis

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Considerable progress in research and clinical application has been made since the original guidelines for managing mucositis in cancer patients were published in 2004, and the first active drug for the prevention and treatment of this condition has been approved by the United States Food and Drug Administration and other regulatory agencies in Europe and Australia. These changes necessitate an updated review of the literature and guidelines. Panel members reviewed the biomedical literature on mucositis published in English between January 2002 and May 2005 and reached a consensus based on the criteria of the American Society of Clinical Oncology. Changes in the guidelines included recommendations for the use of palifermin for oral mucositis associated with stem cell transplantation, amifostine for radiation proctitis, and cryotherapy for mucositis associated with high-dose melphalan. Recommendations *against* specific practices were introduced: Systemic glutamine was *not* recommended for the prevention of gastrointestinal mucositis, and sucralfate and antimicrobial lozenges were *not* recommended for radiation-induced oral mucositis. Furthermore, new guidelines suggested that granulocyte–macrophage-colony stimulating factor mouthwashes *not* be used for oral mucositis prevention in the transplantation population. Advances in mucositis treatment and research have been complemented by an

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increased rate of publication on mucosal injury in cancer. However, additional and sustained efforts will be required to gain a fuller understanding of the pathobiology, impact on overall patient status, optimal therapeutic strategies, and improved educational programs for health professionals, patients, and caregivers. These efforts are likely to have significant clinical and economic impact on the treatment of cancer patients. ***Cancer*** **2007;109:820–31.** *© 2007 American Cancer Society.*

KEYWORDS: cancer therapy, clinical practice guidelines, mucosal barrier injury, mucositis (alimentary, gastrointestinal [GI], oral), mucositis pathogenesis.

In 2004, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) published 2 articles as a supplement in the journal *Cancer*. The first article addressed the pathogenesis, measurement, epidemiology, and consequences for patients of oral and GI mucositis[1]; the second article provided evidenced-based clinical practice guidelines for the management (prevention and treatment) of the condition.[2] However, few specific guidelines were possible based on the published literature available at that time. We anticipated that an updated review would be required approximately every 3 years given the pace and direction of advances in the field: The current report represents the first such update.

Management strategies for oral and GI mucositis increasingly are driven by key scientific advances. These strategies are setting the stage for regulatory approval of drugs and devices, which, in turn, provide opportunities for multidisciplinary expert panels to produce evidence-based guidelines. Table 1 shows the history of mucositis research over the last 40 years and delineates the temporal relations between important developments in scientific discovery, pharmaceutical products, cancer treatment and supportive care, and related professional organizations, conferences, regulations, protocols, and guidelines. Such factors are likely to have had multidirectional influence on the growth of this field, resulting in incremental gains as well as sudden significant advances.

Mucositis remains a morbid side effect of many anticancer treatments. Alimentary mucositis (AM) is a term we recommend to describe cancer therapy-associated mucosal injury of the alimentary tract (mouth to anus). This unifying term acknowledges the similarities along the entire GI tract while allowing for regional differences that require discussion of oral and GI mucositis separately at times based on pathophysiologic responses and clinical characteristics.

MATERIALS AND METHODS

Panel Composition

Our panel consisted of 30 mucositis-involved health care professionals, including oral oncologists, radiation oncologists, medical oncologists, surgeons, nurses, dentists, dental hygienists, basic scientists, epidemiologists, outcomes researchers, and a medical librarian.

Data Collection

Using the Ovid interface to Medline and a publication time frame of January 2002 to May 2005, we retrieved 3974 articles, only 622 of which were of sufficient quality and relevance to be included in our final recommendations. At the time of the search, *mucositis* was not a Medical Subject Heading (MeSH); thus, we searched for *mucositis* as a text word in article titles and abstracts. We also searched for the following terms to identify all publications that had addressed mucositis: *stomatitis*, a MeSH that we exploded to include related terms of *Stevens-Johnson syndrome* and *stomatitis* (*aphthous*, *denture*, *herpetic*); *mucous membrane*, a MeSH that we exploded to include related terms of *gastric mucosa*, *goblet cells*, *intestinal mucosa*, *mouth mucosa*, and *respiratory mucosa*.

We modified terms further with *pathology*, *pathophysiology*, and *radiation effects and injury* to narrow the retrieval to publications in which the mucosa was injured and to limit the search to specific subject areas that were assigned to the various reviewers. By exploding the MeSH term *neoplasms*, we limited the search to neoplastic disease. Our final step was to limit the retrieval to articles that were written in English.

Literature Review

The medical librarian conducted separate literature reviews, working closely with the group leaders for each of 8 subject domains: 1) epidemiology, economics, and outcome; 2) pathogenesis; 3) terminology, definition, and scales; 4) growth factors and cyto-

TABLE 1
History of Developments Significant to Mucositis

Date	Guidelines	Regulatory/conferences	Societies	Products	Scientific advances	Cancer treatments	Supportive care
1960				Hickman lines	Trier GI studies		
1965				Mouth washes/analgesics			
1970						TBI	Antibiotics, transfusion
1975				Chlorhexidine, sucralfate		Chemotherapy, RT	
1980	CE course; local protocols			Loperamide		Transplantation	Stem cell factor; colony-stimulating factors
1985			SOO	3D RT and blocks, ice chips, benzydamine		Newer chemotherapy drugs	
1990	Consensus conference: oral complications		ISOO			Irinotecan, minitransplantations	Febrile neutropenia protocols
1995			MASCC/ISOO/MSG	Laser, octreotide, ranitidine, omeprazole	Four-phase model, stem cells, hamster cheek-pouch		5HT-3 antagonists, antiemetic guidelines
2000	Joanna Briggs, Bethesda, Houston, Cancer Supplement	Bethesda meeting, Houston meeting	GI section of MSG		Whole-depth epithelial/ subepithelial interaction	Targeted therapy, IMRT, IGRT	NK-1 inhibitors, mucositis guidelines
2005	Geneva; current study	Palifermin approval		Palifermin, saforis, gelclair, WGFE, velafermin	Risk prediction, gene mapping, current pathology, tissue microarray, mucositis matrix, alimentary paradigm, 5-phase model		Mucositis and antiemetic guideline updates

GI indicates gastrointestinal; TBI, total body irradiation; RT, radiotherapy; CE, continuing education; SOO, Society for Oral Oncology; 3D, 3-dimensional; ISOO, International Society of Oral Oncology; MASCC, Multinational Association for Supportive Care in Cancer; MSG, Mucositis Study Group; 5HT-3, serotonin; IMRT, intensity-modulated RT; IGRT, image-guided RT; NK-1, neurokinin-1; WGFE, whey growth factor extract.

kines; 5) antimicrobials, mucosal coating agents, anesthetics, and analgesics; 6) alternative and natural therapies, laser, ice, etc; 7) basic oral care, bland rinses, protocol development and education, and good clinical practice; and 8) anti-inflammatory agents and amifostine. Each group reviewed both preclinical and clinical articles relating to the entire alimentary tract. The systematic weighting of both level and grade of evidence followed the same process that was used for the original guidelines based on criteria of the American Society of Clinical Oncology that rated the level of evidence on a scale from I to V and refined this by grading each recommendation from A to D.[3,4] Level I evidence is reserved for meta-analyses of randomized controlled trials or randomized trials with high power. Level II evidence includes randomized trials with lower power, and Level III evidence includes nonrandomized trials, such as cohort or case-controlled series. Level IV evidence includes descriptive and case studies, and Level V evidence includes case reports and clinical examples. Grade A is reserved for Level I evidence or consistent findings from multiples studies of Level II, III, or IV evidence. Grade B is for Level II, III, or IV evidence with generally consistent findings. Grade C is similar to grade B but with inconsistencies; and Grade D implies little or no evidence.

Guideline Development Based on Evidence

We distributed the publications in the finalized set of literature to each group with instructions based on methods for reviewing and scoring the literature published by Hadorn et al.[4] At least 2 panel members reviewed each article. Preclinical studies were not used to create guidelines per se; rather, they were used as indicators of future directions for preclinical and clinical studies. Each group presented its report and draft of guideline revisions at a workshop in Geneva, Switzerland on June 27 and 28, 2005. The entire panel discussed each guideline to ensure that it met the correct standards and to achieve a consensus (see Table 2). The current report includes the new guidelines that were developed based on this process. Each group also has published a companion article in *Supportive Care in Cancer*[5–17] that elaborates on the extent of preclinical and clinical literature in a particular area.

Conflict of Interest and Financial Disclosure

The costs for the workshop and for administrative assistance in guideline preparations were paid from unrestricted educational grants made to the Mucositis Study Group of MASCC/ISOO. No representatives from any of the companies that provided grants attended the workshop, nor were they allowed access to the guidelines prior to publication. The guideline-development process was determined entirely by the panel. Each panel member completed a conflict-of-interest disclosure form that revealed all relationships with pharmaceutical companies that could be affected by the development and publication of these guidelines.

TABLE 2
Guideline Classification and Hierarchy*

Recommendation	A recommendation is reserved for guidelines that are based on Level 1 or Level 2 evidence.
Suggestion	A suggestion is used for guidelines that are based on Level III, Level IV, and Level V evidence; this implies panel consensus on the interpretation of this evidence.
No guideline possible	No guideline possible is used when there is insufficient evidence on which to base a guideline; this conclusion implies 1) that there is little or no evidence regarding the practice in question, or 2) that the panel lacks a consensus on the interpretation of existing evidence.

* Used with permission from the publisher. Adapted from: Somerfield M, Padberg J, Pfister D, et al. ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. *Classic Pap Curr Comments.* 2000;4:881–886.[4]

Future Plans

Revision plan

The panel will continue to review the literature every 2 to 3 years and will publish updates to guidelines as necessary. The current process has created the opportunity for Web-based storage of the publication inventory as well as for future reviews.

Outcomes assessment

In recognition of the importance and challenge of disseminating and using these guidelines in clinical oncology practice, the review team is considering cooperative strategies with other professional oncology organizations as well as methodologies to assess the scope and durability of the impact of the guidelines on clinical practice.

RESULTS

Biologic Basis and Pathogenesis

Efforts to understand the biological basis for AM include research of mechanism-based therapy, risk prediction, long-term toxicity, and associations with other side effects of cancer treatment. GI toxicities from the targeted cancer therapies have yet to be included in this field. It is likely that there are macroscopic factors as well as molecular or cellular factors that are fundamental to the expression of GI toxicity, that both categories are generic or specific,[7] and that

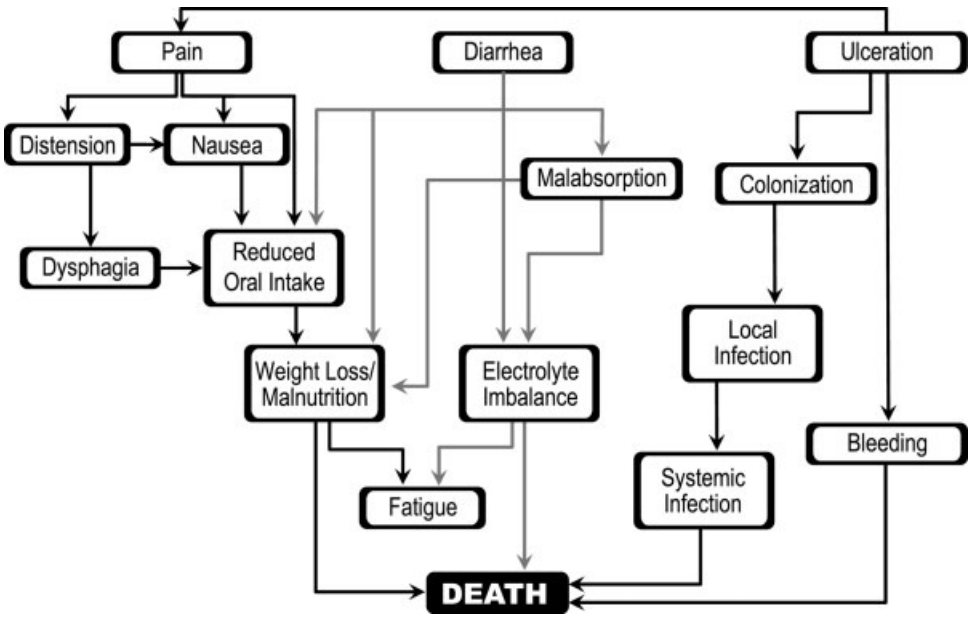

FIGURE 1. Constellation of symptoms and clinical manifestations of gastrointestinal mucositis.

they will provide opportunities for intervention. In the future, it may be possible to predict an individual patient's risk of particular toxicities from radiotherapy and from each different chemotherapy or combination therapy. We recommend future research into mucotoxicity that focuses on identifying its generic and tissue-specific causes, analyzing its genetic components using genetic versus nongenetic controls, and establishing evidence-based grading for and hierarchical characterization of mucotoxicity.

Clinical Mucositis Assessment Scales

Advancements in terminology and in the assessment of AM in patients receiving cytoreductive cancer therapies have resulted in better patient management practices and enhanced drug development to reduce toxicity. Factors of note since publication of the original guidelines in 2004 include: 1) publication of the Common Terminology Criteria for Adverse Events version 3.0,[18] which defines a comprehensive, multimodality grading system for both acute and chronic effects of cancer treatment; 2) implementation of the term *mucositis* as a MeSH category, effective January 2006, which will improve future search capabilities and increase the visibility of the term during related searches (this change was a direct result of a recommendation to the National Library of Medicine in February 2005 by the review group from the original Mucositis Guideline Project and, thus, represents an important outcome of the original project); 3) publication and presentation of additional models depicting the potential impact of oral and GI mucositis relative to symptom clusters[19–26] (although the models have continued to characterize oral and GI mucositis as a continuum of injury rather than biologically and clinically independent toxicities,[23,27,28] new models for the assessment of genetic risk for mucositis[29] and the totality of impact for the condition[23] may develop as research in this area progresses); 4) development of an epidemiological burden-of-illness study by researchers from the Mucositis Study Group to evaluate the impact of AM on patients after treatment with standard-dose chemotherapy and/or radiotherapy; that study uses patient-reported outcome tools to measure impact and investigates the relations between various patient-reported toxicities as well as the true regimen-related incidence and severity of mucositis.[30] The interrelated mucotoxicities are shown in Figure 1.

Epidemiology and Outcomes

Methods for epidemiology review

Our literature searches did not identify any prospective studies of the incidence of mucosal toxicity associated with standard, multicycle chemotherapy for common solid tumors. Therefore, we reviewed 99 recent clinical trials of standard chemotherapy regimens for non-Hodgkin lymphoma or breast, lung, or colorectal cancer for incidence of severe (grade 3 or 4) oral mucositis, diarrhea, and esophagitis.[8] We aggregated the estimates of incidence using previously described methods[1] and weighted the estimates based on the quality of the adverse event reporting and the sample size for each trial. We assigned quality points for the use of standardized assessment scales, for blinded or independent

TABLE 3
Risk of Grade 3 or 4 Oral Mucositis and Diarrhea by Chemotherapy Regimen*

Regimen	No.		Risk of grade 3 or 4 oral mucositis		Risk of grade 3 or 4 diarrhea	
	Studies	Patients	%	95% CI	%	95% CI
All NHL	19	1444	6.55	5.54–8	1.23	1.15–2.12
NHL-15: NHL regimen 15	1	100	3.00	0.50–7	0.50	0.50–2.00
CHOP-14: Cyclophosphamide, doxorubicin, vincristine, and prednisone	9	623	4.82	3.53–6.78	1.04	0.95–2.15
CHOP-DI-14: Cyclophosphamide, doxorubicin, vincristine, and prednisone (dose-intensified)	4	231	7.85	5.28–11.32	2.36	1.32–4.65
CHOEP-14: Cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone	2	346	10.40	7.23–13.44	0.29	0.29–1.01
CEOP/IMVP-Dexa: cyclophosphamide, etoposide, vincristine, prednisone/ifosfamide, and methotrexate-dexamethasone	3	144	4.17	1.74–7.99	2.78	1.39–5.90
All Breast	21	2766	4.08	3.44–4.85	3.41	2.86–4.224
A→T→C: Doxorubicin, taxane, and cyclophosphamide (administered sequentially)†	4	594	2.29	1.30–3.46	2.53	1.36–3.92
AC→T Doxorubicin, cyclophosphamide, and taxane (administered sequentially)	2	515	2.80	1.40–4.20	1.07	0.27–2.07
A→CT: Doxorubicin, cyclophosphamide, and taxane (administered sequentially)	1	19	5.26	2.63–15.79	5.26	2.63–15.79
A→T: Doxorubicin and taxane (administered sequentially)	2	60	4.17	1.67–10	9.17	4.17–15.83
AT: Doxorubicin and taxane	1	36	8.33	1.39–19.44	1.39	1.39–5.56
FAC (weekly): 5-FU, doxorubicin, and cyclophosphamide	1	30	3.33	1.67–10.00	1.67	1.67–6.67
AC (weekly): Doxorubicin and cyclophosphamide	1	22	13.64	2.27–27.27	2.27	2.27–9.09
Taxol (paclitaxel) (weekly)	2	87	2.87	1.15–6.90	1.15	1.15–4.02
TAC: docetaxel, doxorubicin, and cyclophosphamide	7	1403	4.92	3.83–6.07	4.38	3.27–5.54
All Lung (no XRT)	49	4750	0.79	0.88–1.33	1.38	1.30–1.99
Platinum and paclitaxel	16	2009	0.49	0.52–1.06	1.59	1.08, 2.44
Platinum and paclitaxel (low dose)	1	49	1.02	1.02–4.08	1.02	1.02, 4.08
Platinum and docetaxel	1	38	1.32	1.32–5.26	1.32	1.32, 5.26
Platinum, paclitaxel, and other	7	451	1.47	1.20–3.07	2.80	2.17, 4.54
Platinum, docetaxel, and other	1	83	0.60	0.60–2.41	0.60	0.60–2.41
Gemcitabine and platinum	18	1476	1.08	0.09–1.91	1.08	0.99–1.89
Gemcitabine and paclitaxel	2	109	1.84	1.02–5.33	3.69	2.05–6.97
Gemcitabine and vinorelbine	1	67	0.75	0.75–2.99	2.99	0.75–7.46
Vinorelbine and paclitaxel	1	175	0.29	0.29–1.14	0.29	0.29–1.14
Vinorelbine and platinum	1	203	0.25	0.25–0.99	0.25	0.25–0.99
All Colon	10	898	1.67	1.17–2.67	15.42	13.14–17.82
FOLFOX: 5-FU, leucovorin, and oxaliplatin	5	482	1.35	0.73–2.59	10.06	7.52–12.97
FOLFIRI: 5-FU, leucovorin and irinotecan	2	79	4.43	1.90–9.49	10.13	4.43–16.46
IROX: Irinotecan and oxaliplatin	3	337	1.48	0.59–2.97	24.33	19.59–29.08

95% CI indicates 95% confidence interval; NHL, non-Hodgkin lymphoma; 5-FU, 5-fluorouracil; XRT, radiotherapy.

* Adapted from Jones JA, Avritscher EBC, Cooksley CD, Michelet M, Bekele BN, Elting LS. Epidemiology of treatment-associated mucosal injury after treatment with newer regimens for lymphoma, breast, lung, or colorectal cancer. Support Care Cancer. 2006;14:505–515.[8]

† Taxane is paclitaxel or docetaxel.

assessment of toxicity, and for midcycle assessment of toxicity (as opposed to limiting assessments to those prior to each cycle).

Incidence of mucositis associated with standard, multicycle chemotherapy (with or without radiotherapy) for non-Hodgkin lymphoma and breast, lung, or colorectal cancers

Table 3 shows that standard chemotherapy regimens for non-Hodgkin lymphoma occasionally have resulted in severe oral mucositis (3–10%) or diarrhea (1–3%). Similar rates of AM are observed among women who receive standard doxorubicin- and taxane-based regimens for breast cancer. Severe oral mucositis and severe diarrhea are rare among patients with lung cancer who receive platinum-based doublets and triplets, even when radiotherapy is administered concurrently. However, among these patients, severe (grade 3 or 4) radiotherapy-induced esophagitis has been a major concern, occurring in >15% of patients. Based on several studies[8] that included 280 patients, 18% (range, 14.2–22.9%) of patients who receive carboplatin and paclitaxel plus radiotherapy develop severe esophagitis. The risk of severe esophagitis may be lower (10.6%; range, 2.1–20.2%) among patients who receive amifostine; although this estimate was derived from a single study of 47 patients. Patients with advanced colorectal cancers who receive common chemotherapy regimens have a low risk of severe oral mucositis but a

high risk (16%) of diarrhea overall, which approaches 25% when both irinotecan and oxaliplatin are used. Reports of newly emerging standards of care using targeted therapies for lung and colorectal cancers fell outside the time frame of the current review; thus, the impact of these agents on the risk of mucosal damage and diarrhea has yet to be described.

Updated Clinical Practice Guidelines for the Care of Patients With AM

To provide clinicians with the current recommendations in a single document, the guidelines presented in Table 4 represent the integration of the original guidelines from 2004[2] plus the new guidelines developed at the Geneva workshop. The text below addresses the guideline revisions only. The reader is referred to the original *Cancer* supplement publication for more detail on the original guidelines.[2]

Basic oral care and good clinical practice principles

The results from a survey that was conducted by panel members showed that incorporating management guidelines into routine clinical practice will require the successful dissemination and adoption of the guidelines, which can be achieved by educating relevant target audiences.[14] Barriers to such efforts include challenges to dissemination, knowledge deficits, resistance to changing traditional practices, and a variety of administrative issues.[31] We have addressed some of these barriers through a focus on education, quality-improvement processes, and good clinical practices.

The panel suggests interdisciplinary development of systematic oral care protocols that are geared toward the individual needs of the patient; educational approaches to promulgating them that include the patient, family, and staff; and quality-improvement processes to evaluate them. It also suggests the use of a soft-bristle toothbrush that is replaced on a regular basis. A lack of research in these areas renders outcome assessment an extremely important component of oral supportive care to document the benefits of these practices. The updated guidelines also address good clinical practices that should occur regardless of the amount of research-based evidence.[13]

Guidelines. Based on expert opinion and the limited published literature, the panel recommends the following: Regular assessment of oral pain is essential and should be performed using validated, self-report pain instruments. Topical anesthetics or other agents should be considered to promote oral comfort. Initial and ongoing assessment of the oral cavity is essential using validated instruments that include both patient self-report and professional examination. Use of a preventive oral care regimen should be part of routine supportive care along with a therapeutic oral care regimen if mucositis develops. Regular, systematic, oral care hygiene with brushing, flossing, bland rinses, and moisturizers using a standardized oral care protocol should be implemented for all patients. It is noteworthy that an interdisciplinary approach to oral care (nurse, physician, dentist, dental hygienist, dietician, pharmacist, and others as relevant) will provide the most comprehensive means of providing supportive care. Dental examinations and treatment are important prior to the start of cancer therapy for all patients, especially for those with head and neck cancer, and should continue throughout active treatment and follow-up.

Radiotherapy: Prevention and/or Treatment

Antimicrobial lozenge

Guideline. The panel recommends that antimicrobial lozenges *not be used* for the prevention of radiation-induced oral mucositis (Level II evidence, grade B recommendation). Despite the often postulated role of infection in the pathogenesis of mucositis, no conclusive evidence for it has been published. Two new studies of oral lozenges that contained polymixin, tobramycin, and amphoteracin B or bacitracin, clotrimazole, and gentamicin showed no improvement in the incidence or severity of radiation-induced mucositis.[32,33]

Sucralfate

Guideline. The panel recommends that sucralfate *not be used* for the treatment of radiation-induced oral mucositis (Level II evidence, grade A recommendation). Sucralfate is a mucosal coating agent that has been postulated to offer protection to the mucosa. All studies have been negative in the radiation arena, and the new randomized, controlled trial of sucralfate in radiation treatment has confirmed this lack of benefit, showing no difference between micronized sucralfate and salt and soda mouth washes.[34]

Amifostine

Guideline. The panel suggests that intravenous amifostine at a dose $\geq$340 mg/m^2 daily prior to radiotherapy may prevent radiation proctitis in patients who are receiving standard-dose radiotherapy for rectal cancer (Level III evidence, grade B recommendation). Amifostine is an organic thiophosphate that is used as a normal tissue protector during cytotoxic therapy.[35,36] Most of the amifostine studies that have been published since the initial guidelines were established have been small, single-center studies

TABLE 4
Summary of Evidence-based Clinical Practice Guidelines for Care of Patients With Oral and Gastrointestinal Mucositis (2005 Update)

I. Oral mucositis
- Basic oral care and good clinical practices
  1. The panel suggests multidisciplinary development and evaluation of oral care protocols, and patient and staff education in the use of such protocols to reduce the severity of oral mucositis from chemotherapy and/or radiation therapy. As part of the protocols, the panel suggests the use of a soft toothbrush that is replaced on a regular basis. Elements of good clinical practice should include the use of validated tools to regularly assess oral pain and oral cavity health. The inclusion of dental professionals is vital throughout the treatment and follow-up phases.
  2. The panel recommends patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing HSCT. Regular oral pain assessment using validated instruments for self-reporting is essential.
- Radiotherapy: Prevention
  3. The panel recommends the use of midline radiation blocks and 3-dimensional radiation treatment to reduce mucosal injury.
  4. The panel recommends benzydamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy.
  5. The panel recommends that chlorhexidine not be used to prevent oral mucositis in patients with solid tumors of the head and neck who are undergoing radiotherapy.
  6. The panel recommends that antimicrobial lozenges not be used for the prevention of radiation-induced oral mucositis.
- Radiotherapy: Treatment
  7. The panel recommends that sucralfate not be used for the treatment of radiation-induced oral mucositis.
- Standard-dose chemotherapy prevention
  8. The panel recommends that patients receiving bolus 5-FU chemotherapy undergo 30 minutes of oral cryotherapy to prevent oral mucositis.
  9. The panel suggests the use of 20 to 30 min of oral cryotherapy to decrease mucositis in patients treated with bolus doses of edatrexate.
  10. The panel recommends that acyclovir and its analogues not be used routinely to prevent mucositis.
- Standard-dose chemotherapy: Treatment
  11. The panel recommends that chlorhexidine not be used to treat established oral mucositis.
- High-dose chemotherapy with or without total body irradiation plus HCST: Prevention
  12. In patients with hematologic malignancies who are receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation, the panel recommends the use of keratinocyte growth factor-1 (palifermin) in a dose of 60 μg/kg per d for 3 d prior to conditioning treatment and for 3 d posttransplantation for the prevention of oral mucositis.
  13. The panel suggests the use of cryotherapy to prevent oral mucositis in patients receiving high-dose melphalan.
  14. The panel does not recommend the use of pentoxifylline to prevent mucositis in patients undergoing HSCT.
  15. The panel suggests that GM-CSF mouthwashes not be used for the prevention of oral mucositis in patients undergoing HSCT.
  16. The panel suggests the use of LLLT to reduce the incidence of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT if the treatment center is able to support the necessary technology and training, because LLLT requires expensive equipment and specialized training. Because of interoperator variability, clinical trials are difficult to conduct, and their results are difficult to compare; nevertheless, the panel is encouraged by the accumulating evidence in support of LLLT.

II. GI mucositis
- Basic bowel care and good clinical practices
  17. The panel suggests that basic bowel care should include the maintenance of adequate hydration, and that consideration should be given to the potential for transient lactose intolerance and the presence of bacterial pathogens.
- Radiotherapy: Prevention
  18. The panel suggests the use of 500 mg sulfasalazine orally twice daily to help reduce the incidence and severity of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis.
  19. The panel suggests that amifostine in a dose $\geq$340 mg/m^2 may prevent radiation proctitis in patients who are receiving standard-dose radiotherapy for rectal cancer.
  20. The panel recommends that oral sucralfate not be used to reduce related side effects of radiotherapy; it does not prevent acute diarrhea in patients with pelvic malignancies undergoing external beam radiotherapy; and, compared with placebo, it is associated with more GI side effects, including rectal bleeding.
  21. The panel recommends that 5-amino salicylic acid and its related compounds mesalazine and olsalazine not be used to prevent GI mucositis.
- Radiotherapy: Treatment
  22. The panel suggests the use of sucralfate enemas to help manage chronic radiation-induced proctitis in patients who have rectal bleeding.
- Standard-dose and high-dose chemotherapy: Prevention
  23. The panel recommends either ranitidine or omeprazole for the prevention of epigastric pain after treatment with cyclophosphamide, methotrexate, and 5-FU or treatment with 5-FU with or without folinic acid chemotherapy.
  24. The panel recommends that systemic glutamine not be used for the prevention of GI mucositis.
- Standard-dose and high-dose chemotherapy: Treatment
  25. When loperamide fails to control diarrhea induced by standard-dose or high-dose chemotherapy associated with HSCT, the panel recommends octreotide at a dose $\geq$100 μg subcutaneously, twice daily.
- Combined chemotherapy and radiotherapy: Prevention
  26. The panel suggests the use of amifostine to reduce esophagitis induced by concomitant chemotherapy and radiotherapy in patients with nonsmall cell lung cancer.

HSCT indicates hematopoietic stem cell transplantation; 5-FU: 5-fluorouracil; GM-CSF, granulocyte-macrophage–colony stimulating factor; LLLT: low-level laser therapy; GI, gastrointestinal.

with conflicting results that do not help to delineate the role of amifostine in the reduction of mucositis. However, 4 small studies on the prevention of proctitis in patients receiving radiotherapy for pelvic cancers all showed a reduction in symptoms, suggesting that amifostine may help.[37–40]

Benzydamine hydrochloride

Although no new guideline is possible for benzydamine, because no new trials have been published since the 2004 supplement, it is important to note that a study in the United States sponsored by McNeil had aimed to confirm the results of an earlier randomized, placebo-controlled American/Canadian multicenter trial[41] on which the original guideline was based. However, the McNeil study was stopped early after the receipt of results from an interim analysis and the recommendations of the Data Monitoring Committee.

High-dose Chemotherapy With or Without Total-body Irradiation Plus Hematopoietic Stem Cell Transplantation: Prevention

Palifermin

Guideline. In patients with hematologic malignancies who are receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation, the panel recommends the use of keratinocyte growth factor-1 (KGF1) (palifermin) at a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplantation for the prevention of oral mucositis (Level I evidence, grade A recommendation). In the previous review,[2] clinical studies on growth factors and cytokines for the prevention and treatment of oral mucositis showed inconsistent results, and there was not enough evidence to make any recommendations for clinical practice guidelines.

Recombinant human KGF1 (fibroblast growth factor 7 [FGF-7] or palifermin) is a member of the FGF super class. Initially, the tissue-protective capacity of palifermin was attributed to its mitogenic effect, which results in increased thickness of mucosal epithelium. However, palifermin also up-regulates the expression of transcription factor Nrf2 in keratinocytes, which leads to the up-regulation of genes that encode a series of reactive oxygen species-scavenging enzymes.[42] It stimulates the generation of the anti-inflammatory cytokine interleukin-13 (IL-13), which reduces tumor necrosis factor, a proinflammatory cytokine that plays a key role in the pathogenesis of mucositis. In addition, palifermin exerts antiapoptotic effects and reduces angiogenesis.[43] Palifermin was used to prevent oral mucositis in 2 randomized, controlled studies. Prophylactic intravenous injections were given for 3 days prior to each chemotherapy cycle in a Phase I study. Doses ranged from 1 μg/kg per day to 80 μg/kg per day in 6 different cohorts, and 1 group of patients was given placebo. The drug generally was tolerated well in biologically active doses, and the results suggested a positive effect on oral mucositis.[44] In a double-blind, Phase III, multicenter study in which the effects of palifermin were evaluated in 212 patients with hematologic malignancies who were undergoing a stomatotoxic conditioning regimen in preparation for autologous hematopoietic stem cell transplantation (HSCT), the incidence and duration of clinically meaningful oral mucositis was reduced significantly in patients who were receiving palifermin. Palifermin (60 μg/kg per day) or placebo was administered for 3 consecutive days immediately before the initiation of myeloablation and on Days 0, 1, and 2 after transplantation. Palifermin also favorably affected the incidence of blood-borne infections, the use of parental opioids, and a variety of patient-reported outcomes[45] in a well-conducted, double-blind, randomized, placebo-controlled, multicenter study.

Cryotherapy

Guideline. The panel suggests the use of cryotherapy to prevent oral mucositis in patients who are receiving high-dose melphalan (as a conditioning agent in HSCT; Level II evidence, grade A recommendation). Cryotherapy was recommended in the previous guidelines for the prophylaxis of oral mucositis in patients who were receiving bolus 5-fluorouracil and possibly etidronate (both drugs with short half-lives). Melphalan is another such drug, and the studies, although small, showed consistent results in favor of using cryotherapy,[46,47] which obviously is a cost-effective preventive strategy. For some patients, compliance may be confounded by the physically uncomfortable sensation they experience while holding ice in the mouth for an hour.

Granulocyte–macrophage-colony stimulating factor

Guideline. The panel suggests that granulocyte–macrophage-colony stimulating factor (GM-CSF) mouthwashes *not be used* for the prevention of oral mucositis in patients undergoing HSCT (Level II evidence, grade C recommendation). GM-CSF stimulates cells of the innate immune system in mucosal tissues. GM-CSF for oral mucositis was evaluated in 4 studies[48–51] with conflicting results. However, a randomized, controlled study using a GM-CSF prophylactic mouthwash[51] and another randomized, controlled trial using a GM-CSF mouthwash as a

treatment for oral mucositis in transplantation patients who were receiving high-dose chemotherapy[48] demonstrated no positive effects on the duration or severity of oral mucositis.

Standard-dose and High-dose Chemotherapy: Prevention

Systemic glutamine

Guideline. The panel recommends that systemic glutamine *not be used* for the prevention of GI mucositis because of severe toxicity (Level II evidence, grade C recommendation). Glutamine is an amino acid that is a favored food of the GI tract. It is necessary for cell mitosis. Multiple trials studying its effect on mucositis prevention and treatment in various parts of the alimentary canal have produced conflicting results. Pytlik and colleagues performed a double-blind, randomized trial in 40 bone marrow transplantation patients who received either intravenous alanyl-glutamine dipeptide or placebo[52] and observed that oral mucositis was more severe in the treatment group, although diarrhea was reduced, suggesting a differential effect down the GI tract. However, those authors observed an increase in disease recurrences in the glutamine group with a nonsignificant increase in mortality at 2 years.

DISCUSSION

Major advances in the field of mucositis have occurred over the past 3 years, including increased understanding of the epidemiology and pathobiology of the condition; a realization that symptom clusters occur in patients, suggesting that genetic risk prediction for toxicity soon may be a reality; and the availability of new mechanism-based treatments. The registration of palifermin and the recommendation for its use in the prevention of oral mucositis in the HSCT setting is a first in the field. Other drugs are in development, and rapid progress finally is being made in this under-appreciated area.

In the time after the endpoint for inclusion of studies in the original guidelines (May 2002),[2] the pace of publication of mucositis studies has increased. However, the quality of these studies remains variable, with many studies remaining small, poorly designed, and, thus, unable to answer the questions posed. Some of the recent studies indeed are of high quality, and it is those studies that have led to the important changes in the guidelines (Table 3). New agents continue to be developed. However, the panel is unable to incorporate these agents into the guidelines until peer-reviewed clinical studies appear in the literature.[48–51,53–56] Future guideline reviews will address the outcomes of those studies.

Late-breaking Reports and Agents With Insufficient Evidence for a Guideline

Human KGF2 2 (repifermin) has been withdrawn from study because of poor performance in a Phase II study. The reasons for the poor performance are unclear and may relate to scheduling. It has been reported in a Phase I trial that whey growth factor extract reduced oral mucositis in the HSCT setting compared with historic controls.[56] Well-designed, randomized, controlled trials are warranted before a valid assessment of benefit can be made.

A single Phase III trial of Saforis (L-glutamine in a proprietary oral drug-delivery system) recently showed a reduction in oral mucositis among patients who were receiving anthracycline-based chemotherapy,[57] but further trials have been requested by the United States Food and Drug Administration and are awaited.

RK-0202 is N-acetylcysteine in a proprietary mouth rinse formulation that was studied recently in a Phase II, double-blind, placebo-controlled trial among patients who were undergoing radiotherapy for head and neck cancer. In that trial, RK-0202 significantly reduced the incidence of oral mucositis (World Health Organization and National Cancer Institute clinical grade >2) by 29% ($P = .04$) and 46% ($P = .005$), respectively, compared with placebo.[58]

Lessons Learned and Future Directions

Updating the management guidelines for mucositis has been a productive enterprise, reflecting the published evidence to improve clinical practice in mucositis management. The publication of guidelines is only the first step toward ensuring that all patients have access to evidence-based protocols for the management of their potential mucositis. Work needs to be done on promulgation of the guidelines; development of protocols that are based on them; education of patients, caregivers, and staff; and assessment of outcomes from their use. Improved risk assessment needs to occur as well as continued research at the basic and clinical levels into epidemiology, burden of illness, cost of care, prevention, and treatment.[16] Most patients are not followed for toxicity for sufficient duration in clinical trials; thus, these problems largely are underestimated. Although progress is being made toward addressing some of these areas, 2 important areas of assessment remain: genetic-based risk and long-term toxicity. New agents, such as palifermin, are expensive and cannot be justified for prevention when the risk of severe mucositis is low. However, if clinicians could predict which patients on standard-dose treatments would suffer mucositis, then the newer, more expensive agents could be targeted in a cost-effective manner.

We anticipate that the new guidelines will need updating in 2 or 3 years, and we look forward to published studies on the burden of illness and risk prediction as well as evaluations of strategies to improve the uptake and use of the guidelines.

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