

Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines

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introduction

Oral and gastrointestinal mucositis due to cancer therapies such as high-dose chemotherapy and/or radiation continues to be an important clinical problem. Fortunately, there have been strategic advances over the past decade relative to understanding the molecular basis of the injury, opportunities for development of drugs and devices to prevent or treat the toxicity. The guidelines are almost unchanged from the version published in the 2010 *Annals of Oncology*.

definition of mucositis

Mucositis is defined as inflammatory and/or ulcerative lesions of the oral and/or gastrointestinal tract. Infectious disease, immune deficiency and medications can be causative. One of the major causes of mucositis is high-dose cancer therapy.

Alimentary tract mucositis refers to the expression of mucosal injury across the continuum of oral and gastrointestinal mucosa, from the mouth to the anus.

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Conflict of interest: Professor Peterson has reported that he is Principal Investigator on an NIH R13 Conference Grant that provided partial support for the symposium 'Oral Complications of Emerging Cancer Therapies', 14–15 April 2009, Bethesda, MD, USA. Production of a JNCI Monograph for the conference publications is being supported via an unrestricted educational grant from Swedish Orphan Biovitrum, which currently owns palifermin. He has also reported that he is a member of the Scientific Advisory Board and a paid consultant for The GI Co., Inc. This company has been responsible for development of recombinant intestinal trefoil factor, for which the phase II study is cited in the literature section (reference 19, J Clin Oncol 2009). Professor Peterson is also a Consultant for Alder BioPharmaceuticals, Inc.; Merck & Co., Inc.; and Otsuka Pharmaceutical Development & Commercialization, Inc. Professor Bensadoun has reported no conflicts of interest in 2011. In 2010, Professor Bensadoun was a consultant for BioAlliance Pharma, Novartis and Amgen. Dr Roila has reported no conflicts of interest.

mucositis incidence and associated complications

incidence of oral mucositis in patients receiving high-dose head and neck radiation

The incidence of World Health Organization (WHO) grade 3 or 4 oral mucositis in patients receiving high-dose head and neck radiation (e.g. 6000–7000 Gy) to the oral cavity approaches 85%, but all treated patients have some degree of oral mucositis. Mucositis is one of the prime limiting factors of chemoradiation for advanced head and neck carcinoma. The oral pain associated with the lesion frequently leads to the need for enteral nutritional support with or without use of a feeding tube or gastrostomy, as well as use of opioids. The objective of this approach is to maintain dose intensity throughout the entire radiation regimen.

incidence of oral and gastrointestinal mucositis in patients undergoing hematopoietic stem cell transplantation

The incidence of WHO grade 3 or 4 oral mucositis can be as high as 75% in patients undergoing hematopoietic stem cell transplantation (HSCT), depending on the intensity of the conditioning regimen used and the use of methotrexate prophylactically to prevent graft-versus-host disease. Management of oral and gastrointestinal mucositis is one of the main challenges during the period of aplasia, with risk of sepsis related to the degree of mucosal barrier breakdown and depth of marrow suppression.

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

Data relative to risk of developing grade 3 or 4 oral mucositis and diarrhea are presented in Table 1. For all tumor sites, chemotherapy with 5-fluorouracil (5-FU), capecitabine or tegafur leads to a high rate (e.g. 20–50%) of alimentary tract mucositis. Phase I modeling of drug dose and sequence may be of benefit to future patients in this regard. Chemotherapy with

Table 1. Risk of grade 3–4 oral mucositis and diarrhea by some frequently used chemotherapy regimens

Regimen	No. of studies	No. of patients	Risk of grade 3–4 oral mucositis (%)	Risk of grade 3–4 diarrhea (%)
All NHL	19	1444	6.55	1.23
NHL-15: non-Hodgkin lymphoma regimen 15	1	100	3.00	0.50
CHOP-14: cyclophosphamide + doxorubicin + vincristine + prednisone	9	623	4.82	1.04
CHOP-DI-14: cyclophosphamide + doxorubicin + vincristine + prednisone, dose-intensified	4	231	7.85	2.36
CHOEP-14: cyclophosphamide + doxorubicin + vincristine + etoposide + prednisone	2	346	10.40	0.29
CEOP/IMVP-Dexa: cyclophosphamide + etoposide + vincristine + prednisone/ifosfamide + methotrexate-dexamethasone	3	144	4.17	2.78
All breast	21	2766	4.08	3.41
A/T/C, doxorubicin taxane, cyclophosphamide administered sequentially	4	594	2.29	2.53
AC/T doxorubicin + cyclophosphamide, taxane administered sequentially	2	515	2.80	1.07
A/CT doxorubicin, cyclophosphamide + taxane administered sequentially	1	19	5.26	5.26
A/T doxorubicin, taxane administered sequentially	2	60	4.17	9.17
AT doxorubicin + taxane	1	36	8.33	1.39
FAC (weekly): 5-FU + doxorubicin + cyclophosphamide	1	30	3.33	1.67
AC (weekly): doxorubicin + cyclophosphamide	1	22	13.64	2.27
Taxane paclitaxel (weekly)	2	87	2.87	1.15
TAC: docetaxel + doxorubicin + cyclophosphamide	7	1403	4.92	4.38
All lung (no radiotherapy)	49	4750	0.79	1.38
Platinum + paclitaxel	16	2009	0.49	1.59
Platinum + paclitaxel (low dose)	1	49	1.02	1.02
Platinum + docetaxel	1	38	1.32	1.32
Platinum + paclitaxel + other	7	451	1.47	2.80
Platinum + docetaxel + other	1	83	0.60	0.60
Gemcitabine + platinum	18	1476	1.08	1.08
Gemcitabine + paclitaxel	2	109	1.84	3.69
Gemcitabine + vinorelbine	1	67	0.75	2.99
Vinorelbine + paclitaxel	1	175	0.29	0.29
Vinorelbine + platinum	1	203	0.25	0.25

Table 1. (Continued)

Regimen	No. of studies	No. of patients	Risk of grade 3–4 oral mucositis (%)	Risk of grade 3–4 diarrhea (%)
All colon	10	898	1.67	15.42
FOLFOX: 5-FU + leucovorin + oxaliplatin	5	482	1.35	10.06
FOLFIRI: 5-FU + leucovorin + irinotecan	2	79	4.43	10.13
IROX: irinotecan + oxaliplatin	3	337	1.48	24.33

Updated and modified from Keefe DM, Schubert MM, Elting LS et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; 109: 820–831. With permission.

Use of primary prophylactic G-CSF with TAC regimens has been associated with significant reduction in toxicity, including mucositis. Taxane is paclitaxel or docetaxel; 5-FU is 5-fluorouracil.

methotrexate and other antimetabolites leads to a 20–60% rate of alimentary tract mucositis according to the drug's given dose per cycle.

A new trajectory for oral mucositis-like lesions is beginning to be documented in selected patients receiving molecularly targeted therapies [e.g. mTOR (mammalian target of rapamycin) inhibitors and tyrosine kinase inhibitors]. Preliminary reports indicate that the oral lesions can be frequent (e.g. 66% in patients receiving deforolimus) Although it is not clear whether the pathogenesis of these lesions is comparable with mucositis caused by conventional cancer therapies, current mucositis management guidelines as described below may be useful. Further research is needed relative to optimal strategies for prevention and treatment of these mucosal toxicities.

risk factors for mucositis

Risk of mucositis has classically been directly associated with modality, intensity and route of delivery of the cancer therapy. Combination therapy (e.g. head and neck radiation with concurrent chemotherapy) may increase the severity of oral mucositis. Interestingly, the incidence and severity of acute mucosal toxicity has not generally been significantly reduced by utilization of state-of-the-science radiation technologies (e.g. volumetric-modulated arc therapy).

While this modeling continues to be valid, there appear to be additional risk factors (e.g. genetic polymorphisms) in some cohorts that account for the degree of clinical expression. Further study of these more recently defined factors will likely strategically advance the pathobiological model in relation to clinical expression of the toxicity.

Among patient-related risk factors, co-morbidities (e.g. malnutrition) can contribute important risk. All patients should be screened for nutritional risk and early enteral nutrition initiated in the event that swallowing difficulties develop. In addition, patients who develop clinically significant salivary hypofunction/xerostomia due to head and neck radiation and/or antiemetic drugs may experience increased discomfort from oral mucositis. Hydration of the oral mucosa and topical pain interventions such as local anesthetics should be considered.

mucositis assessment

A variety of assessment scales exist for measurement of oral mucositis. Two of the most commonly utilized scales are the WHO and National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scales:

WHO scale for oral mucositis

- Grade 0 = No oral mucositis
- Grade 1 = Erythema and soreness
- Grade 2 = Ulcers, able to eat solids
- Grade 3 = Ulcers, requires liquid diet (due to mucositis)
- Grade 4 = Ulcers, alimentation not possible (due to mucositis)

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

- Grade 1 = Asymptomatic or mild symptoms; intervention not indicated.
- Grade 2 = Moderate pain; not interfering with oral intake; modified diet indicated
- Grade 3 = Severe pain; interfering with oral intake
- Grade 4 = Life-threatening consequences; urgent intervention indicated
- Grade 5 = Death

Most of the scales that are utilized for clinical care incorporate the collective measurement of oral symptoms, signs and functional disturbances. In comparison, some scales are primarily centered in clinician-based observation of mucosal tissue injury (e.g. erythema, ulceration). These latter scales have particular value in clinical trial-based assessment of oral mucositis.

In contrast, there are a limited number of instruments available for assessment of gastrointestinal mucositis. These scales typically measure indirect outcomes of mucosal injury, including diarrhea. However, interpretation of such data can be confounded by other clinical conditions and interventions that also contribute to the event being measured. New technologies may lead to enhanced assessment strategies for gastrointestinal mucositis.

mucositis management guidelines

Oral and gastrointestinal mucositis management guidelines are summarized below, as developed by the Mucositis Study Group of MASCC/ISOO.

oral mucositis guidelines

basic oral care and good clinical practice

- Multidisciplinary development and evaluation of oral care protocols that include frequent use of non-medicated oral rinses (e.g. saline mouth rinses 4–6 times/day) is recommended. Patient and staff education in the use of such protocols is recommended for reduction of severity of oral mucositis from chemotherapy and/or radiation therapy [III, B].
- Alcohol-based mouth rinses should be avoided.
- Interdisciplinary development of systematic oral care protocols is suggested. As part of the protocols, the use of a soft toothbrush that is replaced on a regular basis is also suggested consistent with good clinical practice.
- Patient-controlled analgesia with morphine is recommended as the treatment of choice for oral mucositis pain in patients undergoing HSCT [I, A]. Regular oral pain assessment using validated instruments for self-reporting is essential.
- Because of the high risk of malnutrition following a high-dose chemoradiotherapy regimen, all treated patients should be screened for nutritional risk and early enteral nutrition started in the case of swallowing problems.
- Topical anesthetics can provide short-term pain relief for oral mucositis on an empiric basis.

Prevention of oral mucositis.
radiotherapy.

- Use of midline radiation blocks and three-dimensional radiation treatment to reduce mucosal injury is recommended [II, B].
- Benzylamine oral rinse for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy is recommended [I, A]. Although widely available internationally, including many European countries, it is not available in the USA.
- Chlorhexidine is not recommended for prevention of oral mucositis in patients with solid tumors of the head and neck and who are undergoing radiotherapy [II, B]. (See ‘Treatment of oral mucositis’.)
- Antimicrobial lozenges are not recommended for prevention of radiation-induced oral mucositis [II, B].

standard-dose chemotherapy.

- Oral cryotherapy is recommended for prevention of oral mucositis in patients receiving bolus 5-FU chemotherapy [II, A].
- Oral cryotherapy is suggested to decrease mucositis in patients treated with bolus doses of edatrexate [IV, B].
- Inclusion of granulocyte colony-stimulating factor in TAC (docetaxel + doxorubicin + cyclophosphamide) regimens for breast cancer has been associated with significant reduction in toxicities, including mucositis (stomatitis).
- Acyclovir and its analogs intravenously (i.v.) are not recommended to prevent mucositis caused by standard-dose chemotherapy [II, B]. However, antivirals may be indicated to treat a newly emergent or recurrent oral viral infection that may co-exist with mucositis.

- Palifermin (keratinocyte growth factor-1) i.v. has been studied in solid tumor cohorts, although additional studies are warranted prior to reaching clinical recommendations.

One study suggested that palifermin may be useful in a dose of 40 µg/kg/day for 3 days for prevention of oral mucositis in patients receiving bolus 5-FU plus leucovorin.

Another study reported the efficacy and safety of single-dose palifermin (180 µg per kg body weight) administered 3 days before each chemotherapy cycle in reducing oral mucositis during multicycle chemotherapy regimens for sarcoma. This dosing schema reduced the incidence and severity of oral mucositis and was well tolerated overall, although most subjects developed thickening of the oral mucosa. As the authors indicate, further research is needed to delineate whether palifermin-associated reduction in oral mucositis will enhance adherence to chemotherapy regimens.

Two studies published in June 2011 in the *Journal of Clinical Oncology* added further support to the potential benefit of palifermin in the head and neck cancer setting. In patients undergoing postoperative radiochemotherapy for head and neck, 51% of patients receiving weekly palifermin 120 µg/kg developed severe oral mucositis, vs 67% in the placebo cohort. The second recent study was conducted in definitive chemotherapy regimens of locally advanced head and neck cancer. Patients received 180 µg/kg palifermin or placebo before starting chemoradiotherapy and then once weekly for 7 weeks. The palifermin recipients experienced delayed median time to severe oral mucositis (35 days vs 47 days) and shortened median duration of severe oral mucositis (5 days vs 26 days). The authors of both studies suggest that further study in these cohorts is needed.

high-dose chemotherapy with or without total body irradiation plus HSCT:
prevention.

- Palifermin is recommended in a dose of 60 µg/kg/day for 3 days before conditioning treatment and for 3 days post-transplant for the prevention of oral mucositis in patients with hematological malignancies receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation [I, A].
- Oral cryotherapy is suggested to prevent oral mucositis in patients receiving high-dose melphalan [II, A].
- Topical pentoxifylline is not recommended to prevent mucositis in patients undergoing HSCT [II, B].
- Granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwashes are not suggested for prevention of oral mucositis in patients undergoing HSCT [II, C].
- Low-level laser therapy (LLLT) is suggested 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 [II, B].

Treatment of oral mucositis.
radiotherapy.

- Oral sucralfate is not recommended for treatment of radiation-induced oral mucositis [II, A].

standard-dose chemotherapy:
treatment.

- Chlorhexidine oral rinses are not recommended to treat established oral mucositis [II, A]. Chlorhexidine oral rinses may be an option, however, as a topical antimicrobial to enhance treatment of oral infection based on professional judgment

topical agents also utilized for supportive care treatment oral mucositis. In addition to the approaches described above, some clinicians utilize approved devices for mucositis management. These topically administered agents include Gelclair[®], Caphasol[®] and Biotene[®]. The research evidence base on which these practices are based is limited. However, the agents appear to have an effective safety profile and may be of benefit for some patients.

gastrointestinal mucositis guidelines

basic bowel care and good clinical practice.

In addition to the evidence-based guidelines below, basic bowel care should include maintenance of adequate hydration. In addition, consideration should be given to the potential for transient lactose intolerance and the presence of bacterial pathogens. These suggestions are consistent with good clinical practice.

prevention of gastrointestinal mucositis.
radiotherapy.

- Use of 500 mg sulfasalazine orally twice daily is suggested to reduce the incidence and severity of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis [II, B].
- Amifostine (intrarectal) is suggested in a dose of at least 340 mg/m² to prevent radiation proctitis in those receiving standard-dose radiotherapy for rectal cancer [III, B].
- Oral sucralfate is not recommended 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 gastrointestinal side effects, including rectal bleeding [I,A].
- 5-Amino-salicylic acid and its related compounds mesalazine and olsalazine orally are not recommended to prevent gastrointestinal mucositis [I, A].

standard-dose and high-dose chemotherapy.

- Either ranitidine or omeprazole orally are recommended for prevention of epigastric pain following treatment with standard-dose cyclophosphamide, methotrexate and 5-FU or treatment with 5-FU with or without folinic acid chemotherapy [II, A].
- Systemic glutamine is not recommended for the prevention of gastrointestinal mucositis [II, C].

combined chemotherapy and radiotherapy.

- Amifostine i.v. is suggested to reduce esophagitis induced by concomitant chemotherapy and radiotherapy in patients with non-small-cell lung cancer [III, C].

treatment of gastrointestinal mucositis.
radiotherapy.

- Sucralfate enemas are suggested to help manage chronic radiation-induced proctitis in patients who have rectal bleeding [III, B].

standard-dose and high-dose chemotherapy:
treatment.

- Octreotide is recommended at a dose of at least 100 µg subcutaneously (s.c.) twice daily when loperamide fails to control diarrhea induced by standard-dose or high-dose chemotherapy associated with HSCT [II, A].

source of material

The summary presented above is based on work conducted by members of the Mucositis Study Group of the MASCC/ISOO as well as the authors and the ESMO faculty based on justified standard clinical practice. Additional guidelines are also available from other health professional organizations (e.g. The Cochrane Collaboration). See 'Future directions' below regarding plans to link the MASCC/ISOO mucositis guidelines with guidelines from other health professional organizations over time.

future directions

The mucositis guidelines reported in this version of the ESMO Clinical Recommendations contain few changes in comparison with the previous versions as published in *Annals of Oncology* in 2008 and 2010, respectively.

There continues to be key progress relative to the molecular pathobiology, computational biology and clinical impact of mucosal injury in cancer patients that may generate strategic research and clinical advances in the future. These advances will likely result in revisions in the MASCC/ISOO mucositis guidelines in the next 2–5 years. Examples of novel, important future opportunities based on the recent advances include the following.

- Delineation of predictive models that could enhance the ability of clinicians to identify prospectively which solid tumor patients are at highest risk for development of clinically significant oral and/or gastrointestinal mucositis. Recent research relative to identification of systemic and/or mucosal tissue-based genetic susceptibility for mucositis represents an important example of this modeling.
- Molecular relationships between degree of tumor response and extent of acute mucosal toxicity.
- Enhanced technologies to assess severity of gastrointestinal mucositis.
- Utilization of single or combination topical and/or systemic preventive and treatment interventions, once several molecularly targeted therapies for mucositis are approved for clinical use.
- Increased clinical recognition of the importance of Grade II oral and/or gastrointestinal mucositis, in the context of symptom burdens that are experienced by cancer patients.

- Potential impact of emerging targeted cancer therapies on the incidence and severity of alimentary tract mucositis, including potential unique pathobiology as well as clinical trajectory.

There is also need and opportunity for the conduct of clinical trials relative to devices that have been initially reported as effective and safe in reducing oral mucositis incidence and severity in cancer patients. Such studies are essential for several reasons including (i) validation of current commercial claims; (ii) identification of which patients may experience highest benefit; and (iii) assessment of feasibility for use by these patients.

It is important that basic, translational and clinical research continue relative to preventive and treatment modalities for oral and gastrointestinal mucositis. This collective research could lead to approval of new drugs and devices for which evidence-based, cancer patient-specific identification of risk and associated management of mucositis could become possible.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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