

Management of oral and gastrointestinal mucositis: ESMO Clinical Recommendations

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definition of mucositis

Mucositis is defined as inflammatory lesions of the oral and/or gastrointestinal tract caused by high-dose cancer therapies. Alimentary tract mucositis refers to the expression of mucosal injury across the continuum of oral and gastrointestinal mucosa, from the mouth to the anus.

mucositis incidence and associated complications

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

Incidence of World Health Organization (WHO) grade 3 or 4 oral mucositis in patients receiving high-dose head and neck radiation approaches 100%. Mucositis is one of the prime limiting factors of chemoradiation for advanced head and neck carcinoma, leading frequently to enteral nutritional support and use of morphinomimetics with the objective of maintaining dose intensity throughout the entire radiation regimen.

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

Incidence of World Health Organization (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 GVHD. Management of oral and gastrointestinal mucositis is one of the main challenges during the period of aplasia, with risk of sepsis related to degree of mucosal barrier breakdown and depth of marrow suppression.

incidence of mucositis associated with standard multi-cycle chemotherapy (with or without radiotherapy) for non-Hodgkin's lymphoma and breast, lung or 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. Recently reported phase I modeling of drug dose and sequence may be of benefit to future patients in this regard. Chemotherapy with methotrexate and other antimetabolites leads to a 20–60% rate of alimentary tract mucositis according to the drug's given dose per cycle.

Recent advances in cancer patient management, including utilization of molecularly targeted cancer therapies, are anticipated to strategically redefine cure rates and adverse event profiles in the coming years. Thus the impact of these agents on the risk of mucosal damage and diarrhea has yet to be described.

mucositis management guidelines

Oral and gastrointestinal mucositis management guidelines are summarized below.

oral mucositis guidelines

basic oral care and good clinical practice

- Multidisciplinary development and evaluation of oral care protocols, and patient and staff education in the use of such protocols is suggested for reduction of severity of oral mucositis from chemotherapy and/or radiation therapy [III, B].
- 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.
- In addition to the evidence-based recommendations and suggestions published by MASCC/ISOO, it is relevant to note

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Table 1. Risk of grade 3–4 oral mucositis and diarrhea by chemotherapy regimen

Regimen (4, 13)	No. of studies	No. of patients	Risk of grade 3–4 oral mucositis (%)	Risk of grade 3–4 diarrhea (%)
NHL ALL	19	1444	6.55	1.23
NHL-15: non-Hodgkin's lymphoma regimen 15	1	100	3.00	0.50
CHOP-14: cyclophosphamide + adriamycin + vincristine + prednisone	9	623	4.82	1.04
CHOP-DI-14: cyclophosphamide + adriamycin + vincristine + prednisone, dose-intensified	4	231	7.85	2.36
CHOEP-14: cyclophosphamide + adriamycin + 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
Breast ALL	21	2766	4.08	3.41
A→T→C adriamycin, taxane, cyclophosphamide administered sequentially	4	594	2.29	2.53
AC→T adriamycin + cyclophosphamide, taxane administered sequentially	2	515	2.80	1.07
A→CT adriamycin, cyclophosphamide + taxane administered sequentially	1	19	5.26	5.26
A→T adriamycin, taxane administered sequentially	2	60	4.17	9.17
AT adriamycin + taxane	1	36	8.33	1.39
FAC (weekly): 5-FU + adriamycin + cyclophosphamide	1	30	3.33	1.67
AC (weekly): adriamycin + cyclophosphamide	1	22	13.64	2.27
Paclitaxel (weekly)	2	87	2.87	1.15
TAC: docetaxel + adriamycin + cyclophosphamide	7	1403	4.92	4.38
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
Lung ALL (no XRT)	49	4750	0.79	1.38
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
Colon ALL	10	898	1.67	15.42
FOLFOX: 5-fluorouracil + leucovorin + oxaliplatin	5	482	1.35	10.06
FOLFIRI: 5-fluorouracil + leucovorin + irinotecan	2	79	4.43	10.13
IROX: irinotecan + oxaliplatin	3	337	1.48	24.33

Taxane is paclitaxel or docetaxel.

that topical anesthetics can provide short-term pain relief for oral mucositis on an empiric basis.

radiotherapy: prevention

- Use of midline radiation blocks and three-dimensional radiation treatment to reduce mucosal injury is recommended [II, B].
- Benzylamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy is recommended [I, A].
- Chlorhexidine is not recommended for prevention of oral mucositis in patients with solid tumors of the head and neck who are undergoing radiotherapy [II, B].
- Sucralfate is not recommended for prevention of radiation-induced oral mucositis [II, A].
- Antimicrobial lozenges are not recommended for prevention of radiation-induced oral mucositis [II, B].

standard-dose chemotherapy: prevention

- Thirty minutes of oral cryotherapy is recommended for prevention of oral mucositis in patients receiving bolus 5-FU chemotherapy [II, A].
- Twenty–thirty minutes of oral cryotherapy is suggested to decrease mucositis in patients treated with bolus doses of edatrexate [IV, B].
- Acyclovir and its analogs is not recommended to prevent mucositis caused by standard-dose chemotherapy [II, B].
- In addition to the MASCC/ISOO guidelines published in March 2007, a recent study has suggested that keratinocyte growth factor-1 (palifermin) may be useful in a dose of 40 µg/

kg/day for 3 days for prevention oral mucositis in patients receiving bolus 5-FU plus leucovorin [II, B].

standard-dose chemotherapy: treatment

- Chlorhexidine is not recommended to treat established oral mucositis [II, A].

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 transplant [I, A].
- Cryotherapy is suggested to prevent oral mucositis in patients receiving high-dose melphalan [II, A].
- 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 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]. LLLT may also become useful for management of mucositis caused by high-dose head and neck radiation.

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.

radiotherapy: prevention

- 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 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 are not recommended to prevent gastrointestinal mucositis [I, A].

radiotherapy: treatment

- 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: prevention

- Either ranitidine or omeprazole are recommended for prevention of epigastric pain following treatment with 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].

standard-dose and high-dose chemotherapy: treatment

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

combined chemotherapy and radiotherapy: prevention

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

source of material

This summary is based on work conducted by members of the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (1, 4).

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 experts and the ESMO faculty.

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