Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines

D. E. Peterson¹, R.-J. Bensadoun² & F. Roila³
On behalf of the ESMO Guidelines Working Group*

¹Department of Oral Health and Diagnostic Sciences, School of Dental Medicine, Program in Head and Neck Cancer and Oral Oncology, Neag Comprehensive Cancer Center, University of Connecticut Health Center, Farmington, USA; ²Service d’Oncologie Radiothérapie, Pôle Régional de Cancérologie, CHU de Poitiers, Poitiers, France; ³Department of Medical Oncology, S. Maria Hospital, Terni, Italy

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, and clinical guideline development. The following text addresses this paradigm, with focus on evidence-based guidelines as developed by the Multinational Association of Supportive Care in Cancer (MASCC) in collaboration with the International Society of Oral Oncology (ISOO).

Definition of mucositis

Mucositis is defined as inflammatory and/or ulcerative lesions of the oral and/or gastrointestinal tract usually caused by 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.

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.

While this modelling continues to be valid, there appear to be additional risk factors (e.g. genetic polymorphisms) in some cohorts that account for degree of clinical expression. This latter component of the risk paradigm is under current investigation and is addressed in the ‘Future directions’ section of this report. Further study of these more recently defined factors will likely strategically advance the pathobiological model in relation to clinical expression of the toxicity.

Mucositis assessment

A variety of assessment scales exist for the measurement of oral mucositis. Most of the scales that are utilized for clinical care incorporate the collective measurement of oral symptoms, signs and functional disturbances. By comparison, some scales are primarily centred 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 is a limited number of instruments available for assessment of gastrointestinal mucositis. These scales typically measure indirect outcomes of mucosal injury, including diarrhoea. However, interpretation of such data can be confounded by other clinical conditions and interventions that also contribute to the event being measured. New technologies, as described in ‘Future directions’, may lead to enhanced assessment strategies for gastrointestinal mucositis.

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 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 morphinomimetics, with the objective of maintaining dose intensity throughout the entire radiation regimen.

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

Incidence of WHO grade 3 or 4 oral mucositis can be as high as 75% in patients undergoing haematopoietic 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 the risk of developing grade 3 or 4 oral mucositis and diarrhoea are presented in Table 1. For all tumour sites, chemotherapy with 5-fluorouracil (5-FU), capcitabine or tegafur leads to a high rate (e.g. 20%–50%) of alimentary tract mucositis. Recently reported phase I modelling 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. As described in ‘Future directions’, 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. The impact of these agents on the risk of mucosal damage and diarrhoea has yet to be described.

**mucositis management guidelines**

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

**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 the 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 evidence-based recommendations and suggestions published by the MASC/C/ISOO, it is relevant to note that topical anaesthetics can provide short-term pain relief for oral mucositis on an empirical basis.

**radiotherapy: prevention**

- Use of midline radiation blocks and three-dimensional radiation treatment to reduce mucosal injury is recommended [II, B].
- Benzydamine oral rinse 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 tumours of the head and neck and who are undergoing radiotherapy [II, B].
- Antimicrobial lozenges are not recommended for prevention of radiation-induced oral mucositis [II, B].

**radiotherapy: treatment**

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

**standard-dose chemotherapy: prevention**

- Oral cryotherapy (30 min) is recommended for prevention of oral mucositis in patients receiving bolus 5-FU chemotherapy [II, A].
- Oral cryotherapy (20–30 min) is suggested to decrease mucositis in patients treated with bolus doses of edatrexate [IV, B].
- Acyclovir and its analogues are not recommended to prevent mucositis caused by standard-dose chemotherapy [II, B].

In addition to the MASCC/ISOO guidelines published in March 2007, a study published after the literature reviews were completed suggested that keratinocyte growth factor-1 (palifermin) may be useful in a dose of 40 µg/kg/day for 3 days for prevention of oral mucositis in patients treated with 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 haematological malignancies receiving high-dose chemotherapy and total body irradiation with autologous stem-cell transplantation [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 (GMCSF) 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 centre is able to support the necessary technology and training [II, B].

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.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Risk of grade 3–4 oral mucositis (%)</th>
<th>Risk of grade 3–4 diarrhoea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NHL</td>
<td>19</td>
<td>1444</td>
<td>6.55</td>
<td>1.23</td>
</tr>
<tr>
<td>NHL-15: non-Hodgkin lymphoma regimen 15</td>
<td>1</td>
<td>100</td>
<td>3.00</td>
<td>0.50</td>
</tr>
<tr>
<td>CHOP-14: cyclophosphamide + doxorubicin + vincristine + prednisone</td>
<td>9</td>
<td>623</td>
<td>4.82</td>
<td>1.04</td>
</tr>
<tr>
<td>CHOP-DI-14: cyclophosphamide + doxorubicin + vincristine + prednisone, dose-intensified</td>
<td>4</td>
<td>231</td>
<td>7.85</td>
<td>2.36</td>
</tr>
<tr>
<td>CHOE-P-14: cyclophosphamide + doxorubicin + vincristine + etoposide + prednisone</td>
<td>2</td>
<td>346</td>
<td>10.40</td>
<td>0.29</td>
</tr>
<tr>
<td>CEPD/IPV-Dexa: cyclophosphamide + etoposide + vincristine + prednisone/Ifosfamide + methotrexate = dexamethasone</td>
<td>3</td>
<td>144</td>
<td>4.17</td>
<td>2.78</td>
</tr>
<tr>
<td>All breast</td>
<td>21</td>
<td>2766</td>
<td>4.08</td>
<td>3.41</td>
</tr>
<tr>
<td>A/T/C, doxorubicin taxane, cyclophosphamide administered sequentially</td>
<td>4</td>
<td>594</td>
<td>2.29</td>
<td>2.53</td>
</tr>
<tr>
<td>AC/T doxorubicin + cyclophosphamide, taxane administered sequentially</td>
<td>2</td>
<td>515</td>
<td>2.80</td>
<td>1.07</td>
</tr>
<tr>
<td>A/CT doxorubicin, cyclophosphamide + taxane administered sequentially</td>
<td>1</td>
<td>19</td>
<td>5.26</td>
<td>5.26</td>
</tr>
<tr>
<td>A/T doxorubicin, taxane administered sequentially</td>
<td>2</td>
<td>60</td>
<td>4.17</td>
<td>9.17</td>
</tr>
<tr>
<td>AT doxorubicin + taxane</td>
<td>1</td>
<td>36</td>
<td>8.33</td>
<td>1.39</td>
</tr>
<tr>
<td>FAC (weekly): 5-FU + doxorubicin + cyclophosphamide</td>
<td>1</td>
<td>30</td>
<td>3.33</td>
<td>1.67</td>
</tr>
<tr>
<td>AC (weekly): doxorubicin + cyclophosphamide</td>
<td>1</td>
<td>22</td>
<td>13.64</td>
<td>2.27</td>
</tr>
<tr>
<td>Taxane paclitaxel (weekly)</td>
<td>2</td>
<td>87</td>
<td>2.87</td>
<td>1.15</td>
</tr>
<tr>
<td>TAC: docetaxel + doxorubicin + cyclophosphamide</td>
<td>7</td>
<td>1403</td>
<td>4.92</td>
<td>4.38</td>
</tr>
<tr>
<td>All Lung (no XRT)</td>
<td>49</td>
<td>4750</td>
<td>0.79</td>
<td>1.38</td>
</tr>
<tr>
<td>Platinum + paclitaxel</td>
<td>16</td>
<td>2089</td>
<td>0.49</td>
<td>1.59</td>
</tr>
<tr>
<td>Platinum + paclitaxel (low dose)</td>
<td>1</td>
<td>49</td>
<td>1.02</td>
<td>1.02</td>
</tr>
<tr>
<td>Platinum + docetaxel</td>
<td>1</td>
<td>38</td>
<td>1.32</td>
<td>1.32</td>
</tr>
<tr>
<td>Platinum + paclitaxel + other</td>
<td>7</td>
<td>451</td>
<td>1.47</td>
<td>2.80</td>
</tr>
<tr>
<td>Platinum + docetaxel + other</td>
<td>1</td>
<td>83</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>Lung ALL (no XRT) (continued)</td>
<td>18</td>
<td>1476</td>
<td>1.08</td>
<td>1.08</td>
</tr>
<tr>
<td>Gemcitabine + platinum</td>
<td>2</td>
<td>109</td>
<td>1.84</td>
<td>3.69</td>
</tr>
<tr>
<td>Gemcitabine + paclitaxel</td>
<td>1</td>
<td>67</td>
<td>0.75</td>
<td>2.99</td>
</tr>
<tr>
<td>Gemcitabine + vinorelbine</td>
<td>1</td>
<td>175</td>
<td>0.29</td>
<td>0.29</td>
</tr>
<tr>
<td>Vinorelbine + paclitaxel</td>
<td>1</td>
<td>203</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Vinorelbine + platinum</td>
<td>10</td>
<td>898</td>
<td>1.67</td>
<td>15.42</td>
</tr>
<tr>
<td>FOLFOX: 5-FU + leucovorin + oxaliplatin</td>
<td>5</td>
<td>482</td>
<td>1.35</td>
<td>10.06</td>
</tr>
<tr>
<td>FOLFIRI: 5-FU + leucovorin + irinotecan</td>
<td>2</td>
<td>79</td>
<td>4.43</td>
<td>10.13</td>
</tr>
<tr>
<td>IROX: irinotecan + oxaliplatin</td>
<td>3</td>
<td>337</td>
<td>1.48</td>
<td>24.33</td>
</tr>
</tbody>
</table>

Taxane is paclitaxel or docetaxel.

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 diarrhoea 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 [II, B].

standard-dose and high-dose chemotherapy: prevention

- Either ranitidine or omeprazole is 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].

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 diarrhoea induced by standard-dose or high-dose chemotherapy associated with HSCT [II, A].

combined chemotherapy and radiotherapy: prevention

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

source of material

The summary presented above is based on work conducted by members of the Mucositis Study Group of MASCC/ISOO. Additional guidelines are also available from other health professional organizations (e.g. The Cochrane Collaboration). See ‘Future directions’ regarding plans to link the MASCC/ISOO mucositis guidelines with guidelines from other health professional organizations over time.

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.

future directions

The mucositis guidelines reported in this version of the ESMO Clinical Practice Guidelines contain few changes in comparison with the previous two versions as published in Annals of Oncology in 2008 and 2009, respectively. The MASCC/ISOO Mucositis Study Group has continued to monitor the literature following publication of its updated mucositis management guidelines in 2007. At the annual meeting of the MASCC/ISOO Mucositis Study Group in June 2009, it was determined that no new guidelines were warranted at the present time, based on the current state of the science as published in the literature.

The group also addressed the importance of discussing future guideline development and integration with colleagues in other health professional organizations and who have created guidelines more recently, in order to extend the dissemination and utilization of evidence-based mucositis management interventions. Next steps are being planned by the Mucositis Study Group in this regard.

In addition, 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 prospectively identify which solid tumour 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 modelling.
- 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.

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 continues 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.

literature