REVIEW ARTICLE

Oral mucosal injury caused by cancer therapies: current management and new frontiers in research

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ABSTRACT

This invited update is designed to provide a summary of the state-of-the-science regarding oral mucosal injury (oral mucositis) caused by conventional and emerging cancer therapies. Current modeling of oral mucositis pathobiology as well as evidence-based clinical practice guidelines for prevention and treatment of oral mucositis are presented. In addition, studies addressing oral mucositis as published in the Journal of Oral Pathology and Medicine 2008–2013 are specifically highlighted in this context. Key research directions in basic and translational science associated with mucosal toxicity caused by cancer therapies are also delineated as a basis for identifying pathobiologic and pharmacogenomic targets for interventions. This collective portfolio of research and its ongoing incorporation into clinical practice is setting the stage for the clinician in the future to predict mucosal toxicity risk and tailor therapeutic interventions to the individual oncology patient accordingly.


Keywords: cancer therapy; oral mucositis; pathobiology; prevention; research; treatment

Introduction

Oral mucosal injury caused by cancer therapies (oral mucositis [OM]) is a common toxicity of antineoplastic drugs and/or head and neck radiation in cancer patients (1). OM can result in significant pain and the patient often requires systemic narcotics for pain relief. The lesion can also negatively affect diet, nutrition, oral hygiene, and quality of life. In immunosuppressed patients, secondary infection of oral mucositis lesions can lead to bacteremia, fungemia, and sepsis. In selected patients, the significant morbidity associated with OM may result in dose reductions, delays, and/or treatment interruptions in cancer therapy which in turn can negatively impact patient survivorship. Management of OM has for several decades and continues to be directed to supportive care including basic oral care, oral pain control, prevention and treatment of infection, and nutritional support. The lesion continues to represent an important unmet medical need in oncology practice.

Depending on type and mechanism of action, the cancer treatment regimens can also impact other mucosal sites of the alimentary tract including the esophagus, stomach, and small and large intestine. Oral and gastrointestinal mucositis can cause hospital admission and is thus also associated with increased use of healthcare resources (2).

This invited update provides a summary of oral mucosal injury induced by cancer therapies, including recent advances in pathobiology, evidence for prevention and treatment, and emerging frontiers in research.

Methods

Original research as well as review articles identified in MEDLINE/PubMed was considered for inclusion. In addition, the article database of the Journal of Oral Pathology and Medicine was searched for articles addressing various aspects of oral mucosal injury and related oral complications of cancer therapies published in the period between 2008 and 2013. Key word terms for both searches included the following: oral, mucositis, stomatitis, mucous membrane, mucosa, cancer therapies, chemotherapy, antineoplastic agents, radiation therapy, chemoradiation, head and neck cancer, leukemia, lymphoma, hematopoietic stem cell transplantation, tumor, neoplasm.

The OM clinical guidelines from the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/
ISOO) are also included in this review. Methods utilized by the MASCC/ISOO Study Group to produce the guidelines are described in detail in Bowen et al. (3) and Elad et al. (4). In brief, methodology included a literature search for all relevant papers indexed in Medline until 31st December 2010. In addition, reference lists of previous guidelines papers as well as Cochrane reviews were searched in order to identify potential additional studies. Clinical guidelines were separated based on the aim of the intervention (prevention or treatment of OM), type of treatment (radiotherapy, chemotherapy, chemoradiotherapy, or high-dose conditioning therapy for hematopoietic stem cell transplantation (HSCT)), and route of administration of the OM intervention. Studies were evaluated based on a list of major and minor flaws as described by Hadorn et al. (5). Level of evidence was then assigned for each intervention based on criteria published by Somerfield et al. (6). The resultant clinical guidelines were thus based on the strength of the overall level of evidence for each intervention and were classified into three types: recommendation, suggestion, or no guideline possible.

Pathobiology

The current modeling of OM pathobiology is primarily based on in vitro and animal models that have collectively identified a cascade of events in epithelial and submucosal tissue compartments. As described below, the body of knowledge defines a complex, multifactorial paradigm of mucosal injury and repair (7–20). Selected outcomes of this preclinical modeling have been translated into clinical trials with varying degrees of success, as described later in this section.

A key advance in OM research occurred when Sonis published a five-phase model of OM pathobiology in 1998 (21). This model has been subsequently modified based on new scientific discoveries that have emerged in recent years (Fig. 1). The contemporary model defines a complex pathobiology including microvascular injury, up-regulation of pro-inflammatory cytokines including Tumor Necrosis Factor-α, Interleukin (IL)-1β and IL-6, extracellular matrix reactions and host–microbiome interactions (7, 10, 20, 22–26). It is important to recognize that while selected biologic events may occur sequentially, the collective injury to the epithelium and submucosa can be concurrent. This adversely synergistic interaction results in profound dysregulation of mucosal homeostasis and repair.

In addition to this oral mucosal dysregulation, other oral complications in addition to OM often appear concurrently in patients. The pattern of this collective toxicity profile varies in type, intensity and duration depending upon the type and mechanism of action of the cancer treatment regimen as well as upon patient-specific factors.

As delineated in Journal of Oral Pathology and Medicine publications over the past 5 years the knowledge base regarding mechanisms and interactions among oral complications in oncology patients continues to increase (Table 1). In addition to OM, for example, oral complications may include pain caused by oral cancer, salivary gland hypofunction (objectively decreased saliva secretion)/xerostomia (subjective feeling of dry mouth), fungal infection (27) or

![Figure 1](https://example.com/figure1.png)

**Figure 1** The five-phase model of oral mucositis pathobiology divided into the following: initiation, the primary damage response (messaging and signaling), amplification, ulceration, and healing. Reprinted with permission from Sonis ST. J Support Oncol 2007; 5(Suppl. 4):3–11.
viral infection (28), taste disturbances (dysgeusia) (29, 30), and muscular fibrosis (head and neck radiation patient) (Table 1). As noted in three publications, OM can be exacerbated by colonizing oral microflora when local and systemic immune function is compromised (Table 1) (27, 31, 32). An additional example of these complex and unique oral interactions and their relationship to systemic status is well illustrated in one of the Journal of Oral Pathology and Medicine publications. In this study, neutrophils in oral tissues (oral engraftment) occur earlier in time status/post stem cell transplantation as compared to the time of appearance of neutrophils in the peripheral circulation (blood engraftment) (Table 1) (33). Investigations such as those published in Journal of Oral Pathology and Medicine continue to contribute to identifying new directions in science as well as their potential impact on clinical practice in the future.

In addition to these well-documented toxicities, there are important new directions in the research field that warrant pursuit. For example, the molecular and sensory components associated with oral pain in the OM modeling represent a relatively unexplored frontier. Even though moderate/severe oral pain has long been a clinical hallmark of OM, the specific molecular modeling associated with the symptom has not been systematically studied in detail. Literature developed in non-mucositis cancer pain models (34, 35) could provide powerful information to advance this aspect of the etiopathogenesis in relation to clinical impact. It is important to note that, in the clinical setting, it is often the oral pain and not necessarily the extent of erythema and/or ulceration that is the principal reason that patients require hospitalization as well as expensive supportive care interventions when the mucosal injury develops.

It is also clear in recent years that the patient’s genomic profile can be a key contributor to the cellular and tissue response to cancer treatment (7, 8, 36–39). In this context, novel systems biology approaches as utilized in non-mucositis modeling (40, 41) are increasingly being utilized to systematically delineate key network hubs and pathways that collectively contribute to the OM trajectory (24). Investigative strategies that then link with applied genomics are setting the stage for exciting new advances relative to genome-wide risk prediction that will likely enhance the clinician’s ability to deliver personalized cancer medicine in the future (17). These and related recent scientific advances thus continue to enhance the opportunity to delineate the complex pathobiology such that key molecular pathways can be targeted for mucositis therapeutics in the years to come.

These technologies and ‘lessons learned’ from molecular studies of OM caused by conventional cancer treatments such as high-dose chemotherapy or head and neck radiation will likely also have high value in the study of the unique expression of oral mucosal injury recently being described in cancer patients receiving molecularly targeted biologics. These treatments are directed, for example, to inhibitors of angiogenesis or the mammalian target of rapamycin (mTOR), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), or multikinase Abl pathways (42). They are increasingly being documented as causing oral mucosal injury that is distinctly different in incidence, clinical appearance and response to therapy as contrasted with mucositis caused by chemotherapy and/or head and neck radiation. Given the relative recent emergence of the mucositis associated with molecularly targeted cancer agents, there is important need and opportunity for new research regarding causation as well as optimal clinical management strategies.

The research agenda described in this section provides an excellent opportunity for investigators representing the oral pathology and oral medicine sciences to continue at leadership and collaborative levels in the future. The summary of future research directions (‘New frontiers in research’) presented later in this review further delineates these and other opportunities for discovery and clinical translation.

Despite these exciting new directions in the field a word of caution is appropriate at this stage in the discussion. Without question selected aspects of this knowledge base have been effectively translated into clinical drug and device development in recent years, as described above. However, the actual impact on cancer patient care clinically has only been partially successful to date, despite the impressive scientific and translational advances in recent years. Barriers yet to be overcome include the following: (i) the need to further refine the state-of-the-science molecular model, (ii) competing corporate priorities for mucositis vs. non-mucositis therapeutics, and (iii) varying degrees of incorporation of mucositis management technologies across the extensive clinical oncology practice cohort worldwide. Until these rate-limiting issues can be more fully addressed, the future of OM prevention and treatment will be negatively impacted. It is thus essential to incorporate these additional components into the research and clinical planning so as to optimize research and clinical outcomes.

The evidence-base for management of oral mucositis

Oral mucosal toxicity caused by chemotherapy or head and neck radiation

A number of agents and interventions have been studied for prevention and treatment of OM in patients receiving conventional cancer therapies such as high-dose chemotherapy or head and neck radiation. They encompass a wide range of biologic rationales and potential mechanisms relative to the pathogenesis of OM. Having said this and with few exceptions, however, there is in general considerable variability across results.

As noted earlier the evidence-base for various preventive and treatment interventions has been reviewed by the MASCC/ISOO Mucositis Study Group. This has resulted in publication of clinical practice guidelines for OM as recently as 2013, with a goal of enhancing evidence-based oncology care and improving overall cancer treatment outcomes (3, 4, 43–53). Findings the studies were integrated into recommendations or suggestions at three levels: (i) in favor of interventions for OM, (ii) against interventions for OM, or (iii) no guideline possible due to insufficient or conflicting evidence. Given the state-of-the-science this last category was the most prevalent conclusion by the MASCC/ISOO reviewers.
<table>
<thead>
<tr>
<th>Year published</th>
<th>First author</th>
<th>Title of publication</th>
<th>Selected key findings</th>
</tr>
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<tbody>
<tr>
<td>2013 (29)</td>
<td>M. Baharvand</td>
<td>Taste alteration and impact on quality of life after head and neck radiotherapy</td>
<td>Oral tissues with high turnover rates such as taste buds can be damaged by radiation therapy. All head and neck cancer patients had dysgeusia after radiation therapy and 72.2% had total taste loss. Significant changes were observed in concentrations and intensities of perceived taste modalities, mainly salt and bitter followed by sour and sweet. Dysgeusia negatively impacted quality of life.</td>
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<tr>
<td>2012 (32)</td>
<td>S. Elad</td>
<td>The antimicrobial effect of Iseganan HCL oral solution in patients receiving stomatoxic chemotherapy: analysis from a multicenter, double-blind, placebo-controlled, randomized, phase III clinical trial</td>
<td>Oral infections frequently affect immunosuppressed cancer patients and are associated with systemic infections. Topical Iseganan hydrochloride (administered as swish and swallow, six times daily for 21–28 days in patients having myeloablative chemotherapy) significantly reduced the oral total load of aerobic bacteria, streptococci (mainly viridans streptococci and non-hemolytic streptococci), and yeasts. Topical Iseganan has potential as an oral antimicrobial agent in the prevention of infection.</td>
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<tr>
<td>2012 (33)</td>
<td>C. Forster</td>
<td>A non-invasive oral rinse assay predicts bone marrow engraftment and 6 months prognosis following allogeneic hematopoietic stem cell transplantation</td>
<td>A non-invasive oral rinse was used in a hematopoietic stem cell transplant population to monitor oral neutrophil counts. On average, first appearance of neutrophils in oral tissues (oral engraftment) following hematopoietic stem cell transplantation were detected 8.4 days earlier than neutrophils appearing in the blood circulation (peripheral blood engraftment). This finding enabled confirmation of engraftment one week earlier than when using peripheral blood neutrophil counts alone. Oral engraftment marked the beginning of oral mucositis recovery phase. The time span between oral engraftment and peripheral blood engraftment was a predictor of treatment outcome at 6 months following hematopoietic stem cell transplantation. A time span of less than 6 days resulted in 100% of patients having a negative outcome.</td>
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<tr>
<td>2012 (31)</td>
<td>D. Olczak-Kowalczyk</td>
<td>Bacteria and Candida yeasts in inflammation of the oral mucosa in children with secondary immunodeficiency</td>
<td>Oral mucosal damage in immunocompromised patients may increase risk of bacteremia and fungemia. A correlation was found between prevalence of stomatitis or oral mucositis and presence of coagulase-negative Staphylococci, Enterococcus spp., and Candida spp. in an immunocompromised pediatric population (organ transplant recipients on immunosuppressive medications and central nervous system tumor patients having chemotherapy). 56.8% of the cancer patient study population were colonized with oral yeasts. The incidence of oral candidiasis in yeast colonized patients was 29.2% in head and neck cancer, 17% in solid tumors, and 20.5% in hematological malignancies. The majority of infections were caused by Candida albicans; however, one third of patients harbored non-C. albicans species such as C. glabrata which were more resistant to anti-fungal agents. Overall resistance to azoles was 28.2%. No resistance was found for amphotericin B or nystatin. Age and dentures were identified as independent risk factors associated with yeast carriage. Histopathologic examination of circumvallate papillae in mice exposed to a single radiation dose of 15 Gy to the head and neck region showed disappearance of basal cells by day 4 after irradiation followed by a decrease in the number of taste cells by day 8–20, particularly type II taste cells, with recovery by day 24. Preference for sweet taste was decreased in parallel with taste cell number.</td>
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<tr>
<td>2011 (27)</td>
<td>S. Schelenz</td>
<td>Epidemiology of oral yeast colonization and infection in patients with hematological malignancies, head neck and solid tumors</td>
<td>56.8% of the cancer patient study population were colonized with oral yeasts. Staphylococcus and Entercoccus were the main bacteria found. Candida albicans was the most common yeast found. The incidence of oral candidiasis in yeast colonized patients was 29.2% in head and neck cancer, 17% in solid tumors, and 20.5% in hematological malignancies. The majority of infections were caused by Candida albicans; however, one third of patients harbored non-C. albicans species such as C. glabrata which were more resistant to anti-fungal agents. Overall resistance to azoles was 28.2%. No resistance was found for amphotericin B or nystatin. Age and dentures were identified as independent risk factors associated with yeast carriage. Histopathologic examination of circumvallate papillae in mice exposed to a single radiation dose of 15 Gy to the head and neck region showed disappearance of basal cells by day 4 after irradiation followed by a decrease in the number of taste cells by day 8–20, particularly type II taste cells, with recovery by day 24. Preference for sweet taste was decreased in parallel with taste cell number.</td>
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<tr>
<td>2010 (30)</td>
<td>M. Yamazaki</td>
<td>Reduction of type II taste cells correlates with taste dysfunction after X-ray irradiation in mice</td>
<td>The incidence of oral candidiasis in yeast colonized patients was 29.2% in head and neck cancer, 17% in solid tumors, and 20.5% in hematological malignancies. The majority of infections were caused by Candida albicans; however, one third of patients harbored non-C. albicans species such as C. glabrata which were more resistant to anti-fungal agents. Overall resistance to azoles was 28.2%. No resistance was found for amphotericin B or nystatin. Age and dentures were identified as independent risk factors associated with yeast carriage. Histopathologic examination of circumvallate papillae in mice exposed to a single radiation dose of 15 Gy to the head and neck region showed disappearance of basal cells by day 4 after irradiation followed by a decrease in the number of taste cells by day 8–20, particularly type II taste cells, with recovery by day 24. Preference for sweet taste was decreased in parallel with taste cell number.</td>
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<tr>
<td>2009 (28)</td>
<td>M. Djuric</td>
<td>Prevalence of oral herpes simplex virus reactivation in cancer patients: a comparison of different techniques of viral detection</td>
<td>Before chemotherapy, 91.7% of cancer patients were herpes simplex virus 1 (HSV-1) seropositive. Polymerase chain reaction was HSV-1 positive in 71.7% of cancer patients before chemotherapy and 85% after chemotherapy, direct immunofluorescence was HSV-1 positive in 3.3% before and 11.7% after chemotherapy, and cell cultures were positive in 33.3% and 40%, respectively. HSV-2 was not detected. There was no significant difference in HSV positivity between patients with and without oral mucosal lesions prior to and 14 days after initiation of a chemotherapeutic cycle.</td>
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The MASCC/ISOO OM guidelines in favor of interventions to prevent or treat OM include oral care protocols, oral cryotherapy, laser therapy, recombinant human keratinocyte growth factor-1 (palifermin), benzylamine hydrochloride, systemic zinc supplements, and patient-controlled analgesia with morphine/transdermal fentanyl/2% morphine mouthwash/0.5% doxepin mouthwash to treat OM pain. Additional details are presented in Table 2 (45, 47–52). As noted in the Table, each recommendation and suggestion is targeted to a specific cancer treatment regimen (45, 47–52).

Management approaches to oral complications in the out-patient and hospital setting may to some extent rely on tradition or subjective approaches in some clinical practices. These approaches may also be influenced by lack of interdisciplinary sharing of knowledge and collaboration. Interventions implemented out of tradition or customary practice may not be efficient, and may actually prolong or exacerbate the course of the oral complications. In addition to safety and efficacy, cost-effectiveness of a preventive or therapeutic intervention should be a priority consideration. In this context, it is thus equally important to address the evidence against interventions for OM, in addition to addressing the evidence in favor of interventions for OM.

The MASCC/ISOO OM guidelines recommend avoiding the following for prevention of OM:

- use of intravenous glutamine in patients receiving high-dose chemotherapy for HSCT;
- sucralfate mouthwash in head and neck radiation cancer patients/concomitant chemoradiation or chemotherapy. In addition, sucralfate is not recommended for treatment of OM in head and neck radiation cancer patients nor in chemotherapy patients;
- iseganan mouthwash in high-dose chemotherapy for HSCT, or in head and neck radiation cancer patients/concomitant chemoradiation;
- polymyxin/tobramycin/amphotericin B lozenges/paste and bacitracin/clotrimazole/gentamicin lozenges in head and neck radiation cancer patients (51, 52).

Table 2 The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) Evidence-Based Clinical Practice Guidelines in favor of interventions for oral mucositis secondary to cancer therapy (Not included in the table: Recommendations/suggestions against an intervention for oral mucositis and interventions where no guidelines were possible due to insufficient or conflicting evidence) (for details see references (3, 4, 43, 46–52) and http://www.mascc.org/mucositis-guidelines (54))

<table>
<thead>
<tr>
<th>Prevention/treatment approach</th>
<th>Guideline</th>
<th>Level of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral care protocol</td>
<td>Suggestion that oral care protocols be used to prevent OM in all age groups and across all cancer treatment modalities</td>
<td>III</td>
<td>(45)</td>
</tr>
<tr>
<td>Oral cryotherapy</td>
<td>Recommendation that patients receiving bolus 5-FU CT undergo 30-min oral cryotherapy to prevent OM</td>
<td>II</td>
<td>(47)</td>
</tr>
<tr>
<td></td>
<td>Suggestion to use cryotherapy to prevent OM in patients receiving high-dose melphalan, +/- TBI as conditioning for HSCT</td>
<td>III</td>
<td></td>
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<tr>
<td>Laser and other light therapy</td>
<td>Recommendation for laser therapy (wavelength around 650 nm, intensity 40 mW, tissue energy dose of 2 Jcm to) to prevent OM in HSCT</td>
<td>II</td>
<td>(48)</td>
</tr>
<tr>
<td></td>
<td>Suggestion for laser therapy (wavelength of 632 nm) to prevent RT-induced OM without concomitant CT for H&amp;N cancer</td>
<td>III</td>
<td></td>
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<tr>
<td>Cytokines and growth factors</td>
<td>Recommendation for recombinant human keratinocyte growth factor-1 (palifermin), 60 µg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplantation to prevent OM in HD-CT with TBI followed by auto-HSCT</td>
<td>II</td>
<td>(49)</td>
</tr>
<tr>
<td>Anti-inflammatory agents</td>
<td>Recommendation for benzylamine mouthwash to prevent OM in H&amp;N cancer patients receiving moderate dose RT (up to 50 Gy) without concomitant CT</td>
<td>I</td>
<td>(50)</td>
</tr>
<tr>
<td>Natural agents</td>
<td>Suggestion that systemic zinc supplements administered orally may be of benefit to prevent OM in oral cancer patients receiving RT or CT-RT</td>
<td>III</td>
<td>(51)</td>
</tr>
<tr>
<td>Antimicrobials, mucosal coating agents, anaesthetics, and analgesics</td>
<td>Recommendation for patient-controlled analgesia with morphine be used to treat pain due to OM in patients undergoing HSCT</td>
<td>II</td>
<td>(52)</td>
</tr>
<tr>
<td></td>
<td>Suggestion that transdermal fentanyl may be effective to treat pain due to OM in patients receiving conventional CT and HD-CT, +/- TBI</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suggestion that 2% morphine mouthwash may effective to treat pain due to OM in H&amp;N RT patients</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suggestion that 0.5% doxepin mouthwash may be effective to treat pain due to OM</td>
<td>IV</td>
<td></td>
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</table>

OM Oral mucositis, 5-FU 5-fluorouracil, HD high-dose, CT chemotherapy, +/- with or without, TBI Total body irradiation, HSCT Hematopoietic stem cell transplantation, auto-HSCT autologous hematopoietic stem cell transplantation, RT Radiation therapy, H&N Head and neck.

Quality of recommendations based on Hadorn and Somerfield criteria (5, 6): Level of evidence; I: Meta-analysis of multiple well-designed studies. High-powered randomized trials; II: At least one well-designed experimental trial. Low-powered randomized trials; III: Well-designed, quasi-experimental studies (e.g., non-randomized, controlled, single-group, pre–post, cohort); IV: Well-designed, non-experimental studies (e.g., comparative and correlational descriptive and case studies); V: Case reports and clinical examples.

Guideline classification: Recommendation, This is reserved for guidelines based on levels I or II evidence; Suggestion, Guideline based on levels III, IV, V evidence; implies panel consensus on the interpretation of the evidence; No guideline possible, Used with insufficient evidence to base a guideline because (i) little or no evidence on the practice in question or (ii) the panel lacks consensus on the interpretation of existing evidence.
• chlorhexidine mouthwash in head and neck radiation cancer patients;
• granulocyte–macrophage colony-stimulating growth factor (GM-CSF) mouthwash in patients receiving high-dose chemotherapy for HSCT;
• misoprostol mouthwash in head and neck radiation cancer patients;
• systemic pentoxifylline in patients undergoing HSCT;
• systemic pilocarpine in head and neck radiation cancer patients or high-dose chemotherapy for HSCT (45, 49, 50, 53).

Consideration of the specific indication of either prevention or treatment of OM is important when interpreting and implementing the collective guidelines. For example, it has been suggested not to use chlorhexidine mouthwash for the prevention of OM in head and neck cancer patients receiving radiation therapy. However, it may be used on other indication, for example, reduction of oral microbial load (45, 54).

For other OM interventions [e.g., amifostine (46)], no guidelines were possible due to insufficient or conflicting evidence. This outcome also applied to a number of other interventions described above in context of other cancer treatment settings than those defined in the ‘MASCCISOO’ clinical practice guidelines in favor of the interventions. Examples of this disparity include oral cryotherapy, laser therapy and other light therapy, cytokines and growth factors, anti-inflammatory agents, natural agents, antimicrobials, mucosal coating agents, anesthetics and analgesics, and other miscellaneous agents (45, 47–53).

Oral mucosal toxicity of molecularly targeted cancer therapies

The recent advent of molecularly targeted cancer therapies in clinical oncology practice is redefining treatment paradigms for many types of cancers. These agents directed toward blocking of specific molecular receptors or intracellular pathways including vascular endothelial growth factor receptor (VEGFR) inhibitors, multi-targeted tyrosine kinase inhibitors (TKI), and mTOR inhibitors. Despite these molecularly precise mechanisms of action, however, a novel expression of oral mucosal injury distinct from the classic chemotherapy- and radiation-induced OM has also emerged clinically. For example, painful oral ulcerations are a common complication of mTOR inhibitors and resemble aphthous stomatitis, hence have been referred to as mTOR inhibitor-associated stomatitis (mIAS) (55–59). mIAS may potentially result in dose modifications or delay, or discontinuation of the cancer therapy. Further study of this lesion is needed at both the basic science as well as clinical trial level. Until results of such studies become available, high quality systematic evidence is not available for development of evidence-based clinical practice guidelines. In the interim, the clinical management strategy of mIAS is empirically based on drugs that have been used for the prevention and treatment of aphthous stomatitis and includes topical, intralesional, or systemic corticosteroid therapy dependent on severity of the oral lesions (42, 60–62).

New frontiers in research

Based on laboratory and clinical progress highlighted in this review, the next decade of research promises to bring strategic new advances in pathobiologic modeling that in turn can drive development of new mucositis therapeutics and guidelines for use in clinical practice. In addition to studies of mucosal toxicity, novel research collaborations are being fostered in settings in which the basic and translational science associated treatment-induced mucosal toxicity is compared and contrasted with the science of mucosal health and homeostasis as well as naturally occurring mucosal disease such as inflammatory bowel disease. A recent example of this new paradigm in fostering novel research collaborations was the June 2013 first-in-kind Gordon Research Conference Mucosal Health & Disease (63). This new conference brought together basic and translational researchers from the international community, with specific emphasis on defining new research opportunities for emerging investigators.

Table 3 delineates several of important research domains in relation to key research directions and their potential impact on the field. Basic, translational, and clinical research directed to these and related domains could likely produce paradigm-shifting changes in fundamental scientific discovery associated with mucosal homeostasis, injury and repair. In addition, the future research could contribute to development of novel clinical interventions that could strategically enhance cancer patient care while reducing cost of that care. In selected cases, a specific research domain (e.g., systems biology) directly applies to more than one research direction and its potential impact in the field.

Investigators from dental medicine, including oral medicine and oral pathology, continue to collaborate with other basic and clinical scientists as well as oncology clinicians to further create and pursue these opportunities.

Conclusion

The scope and depth of research and its translation to clinical practice for management of OM in oncology patients has strategically escalated over the past 15 years. In addition to delineating new insights into pathobiology of OM, these advances include development of high quality evidence-based guidelines for prevention and management of the lesion in clinical practice.

Despite these advances, however, OM continues to represent an important unmet medical need in many cancer patients receiving mucotoxic cancer treatments. Precise delineation of specific pathobiologic and pharmacogenomic targets for interventions need to be identified in order to enhance quality of cancer care while reducing cost of that cancer treatment. In addition, further development of novel drugs, biologics, and devices is essential to optimizing clinical management of this biologically complex toxicity.

New research directions such as those highlighted in this review will likely in turn position clinicians to predict toxicity risk and tailor therapeutic interventions to the individual patient. This translation of discovery-level
<table>
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<tr>
<th>Research domain</th>
<th>Key research direction</th>
<th>Potential impact on the field</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular modeling</td>
<td>Study of ‘privileged’ mucosal sites that do not typically develop clinical mucosal injury caused by cancer treatment</td>
<td>Discovery of genetic-, molecular-, and cellular-unique characteristics that either provide a protective role at these sites and/or the absence of which increase risk for mucosal injury.</td>
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<tr>
<td>Mucosal homeostasis</td>
<td>Capitalizing upon research technology and research outcomes from studies of naturally occurring mucosal disease, to inform new research strategies for investigation of mucositis</td>
<td>Determination of the degree to which the pathobiology of naturally occurring mucosal diseases is concordant or discordant with the pathobiology of mucositis caused by cancer treatment regimens.</td>
</tr>
<tr>
<td>Naturally occurring mucosal disease</td>
<td>Genetic and immunopathologic governance of oral pain in relation to sensory pathways</td>
<td>Enhanced customization of systematically administered pain prevention and treatment in cancer patients</td>
</tr>
<tr>
<td>Oral pain</td>
<td>Interfacing high throughput sequencing technology with systems biology in order to discern the biodiversity of microbial communities associated with mucositis causation and progression</td>
<td>Novel antimicrobials directed to mucositis prevention and treatment</td>
</tr>
<tr>
<td>Oral mucosa and the oral microbiome</td>
<td>Analysis of the role of patient-based factors, including genomics and proteomics, in contributing to clinical development of oral mucositis</td>
<td>Creation of a priori predictive models for development of oral mucositis, particularly in (i) solid tumor patients receiving multi-cycle chemotherapeutic regimens, or (ii) patients receiving molecularly targeted cancer treatment biologics.</td>
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<tr>
<td>Molecular basis for cancer patient-based variation in incidence and severity of oral mucosal injury</td>
<td>Integrating the etiopathogenic models of mucosal and dermal injury to identify potential shared or unique causative factors</td>
<td>Advances in discovery-level knowledge of mucosal and dermal wound injury and repair &amp; development of therapeutics that could mitigate cancer treatment injury at mucosal as well as dermal sites.</td>
</tr>
<tr>
<td>Shared vs. unique molecular pathobiology: mucosa and skin</td>
<td>Incorporation of computational biology technology to delineate molecular and network pathways hubs that significantly contribute to mucosal injury and repair</td>
<td>Strategic advances in creation of research and clinical models of mucosal homeostasis as well as mucosal toxicity caused by cancer therapeutics</td>
</tr>
<tr>
<td>Systems biology, also see below, Molecular imaging</td>
<td>Development and application of non-invasive molecular imaging technologies at the discovery and clinical level</td>
<td>Novel research outcomes relative to pathobiology as well as enhanced capability to deliver personalized medicine to oncology patients</td>
</tr>
<tr>
<td>Molecular imaging</td>
<td>Further delineation of the pathobiologic basis for mucositis, capitalizing upon bioinformatics and other computational technologies in order to define central network hubs and pathways that drive mucosal injury and repair</td>
<td>Development of (i) a priori prediction of mucositis incidence and severity in a given oncology patient coupled with (ii) customized therapeutic regimens for mucositis prevention and treatment based upon that risk prediction.</td>
</tr>
<tr>
<td>Development of molecularly targeted drugs, biologics, and devices</td>
<td>Systems biology to more comprehensively delineate key molecular and network pathway targets for perturbation and resultant mucositis prevention and/or treatment</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Science into clinical practice guidelines that produce effective, cost-effective outcomes could then transform the vision of personalized medicine into a reality for cancer patients, their families, and their healthcare providers.

References


**Oral mucosal injury caused by cancer therapies**

Jensen et al.
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Conflict of interest
The authors report no conflicts of interest.