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Oral Mucositis: the New Paradigms

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Abstract

Purpose of review—Mucositis has long been viewed as an unavoidable consequence of high-dose chemotherapy and/or radiation. Management has been directed to supportive care including oral pain control, nutritional support, infection treatment and control of diarrhea. While these interventions have been valuable for clinical management, they have not been collectively directed to molecularly targeted prevention and treatment. This review addresses recent advances regarding mucosal injury in cancer patients, with emphasis on symptom clusters, genetically-based tissue susceptibility and risk prediction, imaging technology, and computational biology.

Recent findings—Modeling of symptom clusters in cancer patients continues to mature. Although integration of mucositis into the paradigm is at an early stage, recent reports suggest that important molecular and clinical insights will emerge in this regard. Initial studies of genetic-based tissue risk are also providing a research basis that may lead to clinical risk prediction models.

These advances are in part being engineered via new imaging and computational biology technologies, drawing upon literature in non-mucositis systems. Just as the past decade has been hallmarked by linkage of pathobiology with clinical expression of mucosal toxicity, the next decade promises to identify new molecular interactions and risk prediction models based on novel application of the analytic technologies.

Summary—Recent research has culminated in convergence of molecular pathobiology with models of symptom clusters, genetic-based risk, and imaging and computational biology. The field is poised to further delineate this paradigm, with the goal of development of molecularly targeted drugs and devices for mucositis management.

Keywords

oral and gastrointestinal mucositis; cancer therapies

Introduction

Mucositis in oncology patients represents inflammation of the mucosa caused by high-dose chemotherapy and/or head and neck radiation^{1, 2}. The injury can affect oral and/or

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gastrointestinal mucosa, depending on the cancer treatment regimen being utilized. Over the past 10 years the concept of alimentary tract mucositis has evolved as a unifying paradigm^{3, 4}. Descriptions of the effect of molecularly targeted therapies (e.g., mTOR) on the modeling, including oral mucositis^{5 *}, are now being reported.

Key clinical manifestations of oral mucositis include painful erythema and ulceration. The painful component associated with moderate-severe oral mucositis can be sufficiently severe so as to cause reduction of chemotherapy doses in subsequent multi-cycle regimens and temporary or permanent interruption of radiation therapy^{6, 7}. Patients with oral mucositis are significantly more likely to experience severe pain and weight loss⁸. Severity of oral mucositis has been correlated with compromised swallowing function in patients, resulting in the requirement for feeding via a gastrostomy tube^{6, 9}. Multi-cycle dose modifications have been associated with increased cancer recurrence and decreased survival rates¹⁰.

These and related sequelae can result in hospitalization which in turn can increase cost of care. For example and depending on severity, oral mucositis has been associated with increased costs of \$1,700–\$6,000 per affected patient receiving head and neck radiation¹¹.

Gastrointestinal mucositis can also be a common, important clinical problem^{12 *}. Hallmarks of the lesion include abdominal pain, bloating, and diarrhea. Although supportive care approaches can be efficacious, there is need to develop new approaches for customized therapies analogous to the approach taken for prevention and control of nausea and emesis. Fortunately, important new linkages are being established in the literature relative to molecular causation that is either unique to the gastrointestinal component, or indicative of potentially common causative pathways with those involved in the oral mucositis trajectory^{13, 14 **, 15–16}.

Oral and gastrointestinal mucositis continues to represent an important unmet clinical need.

There is only one United States Food and Drug Administration (FDA)-approved drug for oral mucositis prevention. This drug, palifermin¹⁷, was approved for use in patients with hematologic malignancies and who are undergoing high-dose chemotherapy without or with radiation, followed by hematopoietic stem cell rescue. Thus, palifermin is approved for use in an at-risk population, but one that represents a relatively small number of the total patients who might otherwise benefit from such mucositis therapies. There are no FDA-approved molecularly-targeted drugs to prevent gastrointestinal mucositis.

Thus, new paradigms are needed to comprehensively address the complex relationships among pathobiologic mechanisms, risk for clinical expression, and response to preventive and treatment interventions. Fortunately, the state-of-the-science has positioned the field to achieve major milestones in this modeling over the next five-ten years.

Symptom clusters

The importance of the adverse impact of multiple toxicities of cancer therapy on the cancer patient has become increasingly delineated over the past five years^{18 **, 19, 20, 21 *, 22}. These observations have led to development of the concept of a “symptom burden” for a given patient, in which both severity of the symptoms as well as the patient's perception of impact of the symptoms is relevant¹⁹. In this modeling, the “whole” is indeed greater than the “sum of the parts”. Even mild toxicities (e.g., World Health Organization Grade 2), when occurring in combination, can produce a constellation of injury that can be highly clinically significant. In addition to the clinical implications, such modeling creates important implications with targeting reduction in Grade 2 toxicities in addition to the traditionally-targeted moderate-severe Grade 3 and 4 adverse events.

There are few reports of the role of oral and gastrointestinal mucositis on symptom clusters. Symptom clustering research is a relatively new field, and integration with mucositis modeling is in its early stages. Several important opportunities exist for study, including (i) common molecular pathways; and (ii) impact of direct reduction of one toxicity via drug or device on a secondary reduction of another toxicity. It will be important to consider key research issues as defined Miaskowski et al. in 2007 (Table 1)¹⁸ **.

Genetically-based tissue susceptibility and risk prediction

For many decades it has been observed that different oral mucosal anatomic sites vary in their risk for developing clinically significant oral mucositis. For example, high dose chemotherapy often causes at least moderate mucositis of the buccal mucosa, floor-of-mouth, lateral tongue and soft palate, whereas hard palate and attached gingiva are rarely involved¹. In addition, the classic modeling of uniform commonality among mechanisms for injury across the alimentary tract mucosa are now being challenged by recently emergent data, including a recent study by Logan et al.¹⁴ ** Although the definitive new paradigm is not fully established, these new lines of research are providing insights as to why some chemotherapy regimens are more frequently associated than other regimens with oral and gastrointestinal site-specific mucositis. The recent studies may also offer insight into mechanisms by which specific mucosal sites (e.g, conjunctival mucosa) do not typically develop clinical mucositis while other sites (e.g, buccal mucosa) are often at high risk.

As an example of important recent work in this field, the German 5-FU Toxicity Study Group examined genetic markers for toxicity related to 5-fluorouracil²³ **. A significant genetic association between a DPD splice site mutation (DYPD*2A) and mucositis was observed. These results are consistent with the fact that DPD has been previously shown to rapidly metabolize the majority of 5-fluorouracil that is administered. Of note is that the DPD mutation resulting in DPD deficiency has been described as the major determinant of 5-FU-associated toxicity²⁴.

This line of research links well with previous work by another group that studied thymidylate synthase (TS), an enzyme that synthesizes nucleotides. Elevated TS expression has been associated with enhanced survival among patients receiving 5-FU²⁵. Reduced TS expression in normal colonic mucosa prior to 5-FU administration has been associated with higher incidence of diarrhea, stomatitis, dose reduction and treatment discontinuation following infusion with 5-FU²⁶. Polymorphisms in the TYMS gene promoter that encodes TS are also associated with 5-FU toxicity in colorectal cancer patients²⁷.

This modeling is setting the stage for potential identification of degree of relative risk of patients developing oral and/or gastrointestinal mucositis. It provides a cogent basis for envisioning a scenario in which genetic variations will be evaluated prior to the determination of cancer therapy regimen in order to select treatments that will be tolerable as well as effective²⁸.

Imaging technology

Imaging technology has principally been utilized as a diagnostic tool to evaluate state of health or disease of mucosa. For example, infrared thermography has demonstrated evidence of increased vascularity in patients with mucositis, although the stage of the lesion (e.g. erythema versus ulceration) may be an important confounder relative to signal detection²⁹. Orthogonal polarization spectroscopy has utilized polarized light and real-time video imaging to measure microcirculatory velocity and white blood cell margination in relation to acute inflammation³⁰. Laser Raman Spectroscopy (RS) is based on use of inelastic scattering of monochromatic light and has recently been demonstrated to reliably acquire the

signal from the oral mucosa of patients in reproducible fashion across anatomic oral sites and to determine if the RS signature of normal oral mucosa is reproducible among anatomic oral sites and among subjects of different races and gender³¹. Confocal laser endomicroscopy is a light microscopic technique that permits construction of a 3-dimensional image based on visualization of mucosal histology^{32, 33, 34}. A recent report of sidestream dark-field video microscopy identified alterations in the oral mucosal microvasculature circulation that could represent an important mechanism of early tissue injury³⁵. Narrow band imaging is an optical filter technology that can differentiate between deep and shallow blood vessels, which could provide additional insight into mucosal-based change secondary to cancer therapy^{36, 37}.

A novel application of imaging technology was reported in 2008, in which video-capsule endoscopy was utilized to visualize small intestinal mucosal changes secondary to conditioning chemotherapy in autologous hematopoietic cell transplant patients^{38 *}. Mucosal edema, erosion and ulceration were observed. This innovative application of existing imaging technology may well lead to new insights relative to the relationship between tissue-based change and clinical symptoms.

The recent advances in imaging technology, including those described above, will likely further enhance the understanding of tissue-based changes in form and function, and also provide new opportunities for standardized assessment of mucosal injury in the research setting.

Computational biology

Given the molecular complexity of oral and gastrointestinal mucositis, it is becoming increasingly important to develop new computational strategies to identify the critical molecular network hubs and downstream pathways involved in the pathogenesis of mucositis. This type of conceptual framework has been utilized for other biologic systems^{39 **} and is becoming increasingly relevant to mucosal injury research as well. A systems biology approach can represent a powerful tool, if there is a robust population of molecular data with which to conduct the computational modeling.

This is a relatively new frontier for studying mucosal injury in cancer. A limited number of relatively recent publications exist. For example, Bowen et al. studied the early time course of gene expression in a rat model of gastrointestinal mucositis⁴⁰. At 1 hour post-chemotherapy, early changes included mitogen-activated protein kinase, cell cycle regulation and cytokine receptor signaling, while approximately 72 hours later there were changes to the complement cascade. Sonis et al. characterized the relationship of expressed genes from cRNA in peripheral blood samples from patients undergoing chemoradiation for head and neck cancer. Evaluation of relationships of specific genes, canonical pathways and functional networks demonstrated strong concordance between oral mucositis pathogenic mechanisms in relation to the genes, pathways and networks⁴¹. More recent work by van Erp et al. has demonstrated that the risk for mucosal inflammation was increased in the presence of G allele in CYP1A1 2455A/G in patients receiving single-agent sunitinib^{42 **}. There is also now the opportunity to consider the modeling in the context of molecular-based identified of microflora that heretofore may not have been integrated into the paradigm^{43 **}.

These studies are contributing to the foundation on which comprehensive data analysis of subjects at low, medium and high risk for oral and/or gastrointestinal injury can be studied. This type of research may lead to new paradigms relative to risk prediction for mucositis in the future.

Conclusions

The evidence base for mucositis caused by cancer therapies continues to escalate in scope and volume. The recent application of state-of-the-science imaging and computational technologies from other research fields to the molecular and clinical study of oral and gastrointestinal mucositis is particularly innovative. Based on evolution of clinical and scientific knowledge from other toxicities (e.g., nausea and emesis), it seems probable that the next decade of mucositis research will lead to novel opportunities to predict risk of injury as well as incorporate customized preventive and treatment approaches. These advances could mark a new era for management of mucositis caused by cancer therapies, and thus comprehensively redefine the paradigm of the toxicity that has been observed in cancer patients for over 60 years.

Acknowledgments

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Table 1**Critical considerations in symptom cluster research with oncology patients 18****Conceptual considerations**

- Refinement of the definition of a symptom cluster
- Development of criteria to be used to evaluate the relationship between and among the symptoms that are specified within a cluster
- Use of the term “symptom cluster” to refer to the empiric or de novo identification of symptom clusters using an appropriate statistical procedure (e.g., factor analysis, cluster analysis)
- Use of the term “patient subgroups” (not clusters of patients) to refer to groups of patients with different experiences with a specific symptom cluster that are identified using the appropriate statistical procedure (e.g., cluster analysis, latent profile analysis)
- Determination of the best approaches to evaluate the underlying molecular mechanisms for symptom clusters

Considerations associated with the empiric or de novo identification of symptom clusters

- Comparison of the various statistical approaches to identify symptom clusters
- Comparison of the various methodological approaches to identify symptom clusters
 - Use of symptom severity scores or symptom distress scores to create symptom clusters
 - Number and types of symptoms on the symptom inventory
 - Generic versus disease-specific symptom inventories
- Epidemiologic studies to identify symptom clusters de novo
 - Studies within and across cancer diagnoses
 - Studies within and across cancer treatments
 - Studies within and across stages of disease

Considerations associated with the identification of patient subgroups based on their experiences with a specific symptom cluster

- Determination of the criteria to be used to include various symptoms with a specific symptom cluster
- Determination of the optimal approaches to measure a specific symptom cluster phenotype to insure the most valid and reliable patient subgroups
 - Use of symptom intensity, symptom distress, and/or symptom frequency measures to characterize a specific symptom cluster phenotype
 - Use of a single-item symptom inventory versus a number of symptom-specific questionnaires to characterize a specific symptom cluster phenotype
- Determination of the optimal statistical approaches to identify subgroups of patients based on their experiences with a specific symptom cluster
- Identification of the optimal methods to determine the phenotypic characteristics of patient subgroups with different experiences with a specific symptom cluster
- Identification of the optimal methods to characterize the underlying molecular mechanisms that explain the patient subgroups with different experiences with a specific symptom cluster
- Replication studies of patient subgroups with different experiences with a specific symptom cluster
- Determination of the most sensitive patient outcomes to distinguish among subgroups of patients based on differences in their experiences with a specific symptom cluster