Mucositis in patients with hematologic malignancies: an overview

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ABSTRACT

Mucosal barrier injury (mucositis) is a common complication of many treatments used in hematologic malignancies, affecting most patients whose neoplasms are treated with intensive chemotherapy, and virtually all those receiving myeloablative conditioning regimens prior to hematopoietic stem cell transplantation. Mucositis has been identified as a critical risk factor for infections and is a major driver of analgesic and total parenteral nutrition use. Patients with this complication require careful analgesic therapy, additional nursing care and longer hospitalization. To date, the measures to prevent and treat this potentially devastating complication are inadequate and limited to the control of pain, infections, bleeding and nutrition. Nevertheless, in the last decade, a better insight into the pathogenesis of the mucosal damage has led to the development of novel therapeutic options which potentially could allow a targeted approach to mucositis.

Key words: mucositis, pain, hematologic malignancies, graft-versus-host disease, hematopoietic stem cell transplantation.

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Mucositis is a pathological process characterized by mucosal damage, ranging from mild inflammation to deep ulcerations and affecting one or more parts of the alimentary tract, from the mouth to the anus, as a consequence of radiation therapy and/or chemotherapy.[1] Indeed, for unknown reasons, other mucosae, apart from those lining the mouth and the intestine, generally escape toxicity, with the exception of bladder mucosa after alkylating agents and the conjunctiva after high doses of cytarabine.

Although the mechanisms by which any mucosal injury occurs are likely to be similar, the unique properties of each part of the digestive tract may modify its response to a toxic challenge. The mucosal compartments of the alimentary tract share the same embryogenetic origin, but show different functional and anatomic features, so that two main syndromes may be distinguished: oral mucositis (OM) and gastrointestinal mucositis (GIM).[2] Treatment-induced mucositis is one of the most debilitating and troublesome side effects from the patient's perspective and profoundly influences quality of life (QoL), being associated with a symptom burden including pain,[3] bleeding, dysphagia, infections[5] and food intake impairment, which can result in the need for total parenteral nutrition (TPN).[4] In addition, mucositis is associated with longer periods of hospitalization, significant health and financial costs and may interfere with the regular administration and dosing of programmed treatment plans and with a patient's management.[6,7]

The most important complications associated with mucositis in oncohematologic patients receiving myelosuppressive chemotherapy are infections; indeed, in neutropenic patients mucositis is strongly associated with bacteremia and sepsis due to Gram-negative bacilli such as *Escherichia coli* and *Pseudomonas aeruginosa*, yeasts of the *Candida* species, and Gram-positive cocci, such as *Streptococcus viridans*, as probably happens in patients with

cytarabine-induced mucositis.[8]

In the setting of allogeneic stem cell transplantation (SCT), mucositis plays a contributing role in the development and maintenance of acute graft-versus-host disease (GVHD) through the overproduction of inflammatory cytokines.[9] Moreover, the digestive tract, mainly the small intestine, represents a major target of GVHD, whose manifestations are induced by immune-mediated mechanisms and appear quite similar to those related to cytotoxic treatments, so that GVHD-related mucosal lesions could be considered as a mucositis with a different pathogenesis.[10]

Several forms of oral mucosal damage, such as those related to herpes simplex virus (HSV) and candida infections, can also appear as mucositis.[11]

Finally, other forms of mucosal injury are commonly observed among patients with advanced hematologic malignancies, such as xerostomia and alterations of taste sensation. These injuries reflect the patient's poor performance status and the failure of local regulatory and defense mechanisms.[12]

Anatomy and physiology of the mucosal compartments of the digestive tract

The surface of the mouth can be divided into a masticating part (lined by squamous, stratified and keratinized epithelium), comprising the gums and hard palate, a taste-specialized part, and a non-keratinized part comprising the soft palate, lips, lower tongue and cheek.[13] Non-keratinized epithelium appears stratified, with stem cells in the inner portion, and lies on a thin lamina propria; salivary glands located in the submucosa provide growth and antimicrobial factors and clearing substances. The lamina propria contains cells belonging to the reticulo-endothelial system, which, together with other lymphoid structures localized in the gastrointestinal tract, form the gastrointestinal-associated lymphoid tissue system. The esophageal mucosa consists of stratified squamous epithelium, while a simple cylindrical layer of cells lines the stomach.

The intestinal mucosa is more complex and consists of a single layer of columnar epithelium. The small intestine is characterized by simple cylindrical epithelial cells (enterocytes) and by mucus-producing cells organized in the structure of the villus; at the bottom of each villus there is a glandular crypt; the intestinal stem cell is probably located at the base of the crypt and could give rise to every kind of epithelial cell. The colon and rectum have the same type of epithelium, while the anus appears to be lined by stratified epithelium.

Several cytokines, calcium ions, retinoic acid and vitamin D3 are important stimulatory signals; moreover some peptides, such as TGFα, EGF and trefoil peptide, act as growth and protective factors.[14] Normally, mouth and bowel cells undergo renewal over 7-14 and 4 days, respectively; the differences in cellular turnover may explain why mucositis develops in the intestine earlier than in the mouth following radiotherapy or chemotherapy.

The mouth contains nociceptors with a high threshold and frequency connected to fast A-δ fibers to transmit highly discriminated stimuli; moreover C-type unmyelinated nociceptors transmit a continuous sensation of unspecified pain.[15] Mucosal homeostasis relies on a balance between the differentiation and apoptosis of cells in the upper layers and the mitotic activity of lower layers together with integrin expression, and modulation of adherence.

Epidemiology and causative factors

Mucositis is the result of a pathological process to which treatment-induced and patient-related factors contribute.[2,7,16] The toxicity of each drug depends on its dosage and the time to which a patient is exposed to it, besides its intrinsic properties. Most anticancer drugs reach the mucous membrane through the blood, but some, such as methotrexate and etoposide, can be found in the salivary fluid, thus having a direct effect on epithelium.

Comorbidities, infections, poor oral hygiene and prolonged treatment with steroids are some patient-related factors. Furthermore, differences in drug metabolism, absorption, distribution, and excretion, due to the genetic variants of several families of enzymes, seem to have pronounced effects.[17]

Therefore, significant differences in the severity of mucositis among patients treated with the same chemotherapy regimens may be due to several factors, such as the genetic variations in a patient's pharmacodynamic responses to chemotherapeutic agents. For example, the administration of methotrexate, a highly mucotoxic agent, was associated with different rates of mucositis in patients undergoing allogeneic SCT according to patient's genotype of a polymorphism in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene (C677T); patients with the *MTHFR* TT genotype have lower MTHFR activity and were noted to have more severe mucositis than patients with wild-type enzymes.[18] Moreover, genetic polymorphisms for thiopurine S-methyltransferase are a major factor responsible for large individual variations in both the toxicity and therapeutic effect of thiopurine.[19]

Thus far, there is no predictive model of the risk of mucositis, at the beginning of therapy. However, by exploiting molecular diagnostic methods, pharmacogenomics will eventually allow routine determination of a patient's genotype, enabling the physician to tailor the drug and dosage to the individual patient.

Mucositis following chemotherapy

Some groups of anticancer drugs, alone or in combination, are particularly often responsible for mucositis. The most recorded mucotoxic agents are: thymidine synthetase inhibitors, such as methotrexate, topoisomerase II inhibitors (etoposide, irinotecan); pyrmidine analogs (cytarabine); purine analogs (6-mercaptopurine and 6-thioguanine); alkylating agents at high doses (busulfan,

melphalan and cyclophosphamide); and intercalating drugs (idarubicin, doxorubicin, daunorubicin). When these agents are administered in multiple cycles, the risk of mucositis increases at each course.[7] Following a standard dose-dense chemotherapy for non-Hodgkin's lymphomas (NHL), such as the CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen, the reported incidence of OM is between 2% and 10%; the addition of rituximab and a shorter interval of administration (CHOP-14 regimen) has not been associated with a higher incidence of OM.[20]

In a group of elderly NHL patients, the incidence of OM was reported to be reduced by replacing doxorubicin with epirubicin or mitoxantrone.[21] Among third generation protocols for NHL, OM occurred in 11% of patients who had received MACOP-B therapy (intermediate dose methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) and in less than 3% of those treated with F-MACHOP (fluorouracil, intermediate dose methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and cytarabine).[22] In the setting of Hodgkin's lymphoma, the reported incidence of mucositis was 3% in patients who received the ABVD (doxorubicin, bleomicine, vinblastine and dacarbazine) regimen versus 8% in those treated with hybrid multidrug regimens.[23]

Finally, the mucosal toxicity associated with almost intensified combination regimens given as salvage treatment for lymphoma patients is generally mild and manageable. Patients with acute myeloid leukemia (AML) treated with standard anthracycline-based regimens develop profound myelosuppression and OM (10-15% of cases).[24] In this setting, liposomal daunorubicin seems to reduce the incidence of mucositis,[25] while more aggressive protocols cause a higher incidence: the FLAG (fludarabine, cytarabine, G-CSF) protocol induces mucosal damage in 50% of patients,[26] a rate that rises to 70% in those treated with idarubicin-containing FLAG.[27] In patients with acute promyelocytic leukemia treated with trans-retinoic acid (ATRA), which can cause mucosal dryness, and idarubicin, the incidence of OM is about 10%, as observed in patients treated with an ATRA and idarubicin-containing (AIDA) protocol.[28,29] Hydroxyurea is used as a pre-induction, palliative or mild myelosuppressive drug in AML and has not been associated with mucosal injury. In contrast, among the oral agents available for the treatment of the disease, 6-mercaptopurine is strongly mucotoxic. Finally, some agents currently used in oncohematology, such as interferon and imatinib, do not produce mucosal damage. The frequent watery diarrhea following bortezomib administration is probably due to intestinal neuropathy rather than to mucositis.

Mucositis due to monoclonal antibodies

Gentuzumab-ozogamicin, a monoclonal antibody targeting the CD33 antigen on blast membranes, has no effect on the mucosa, but its use can result in prolonged myelosuppression, so that OM occurs in about 4% of people treated with this agent.[30] Rituximab and alemtuzumab, which are increasingly used in the setting of lymphoproliferative syndromes, do not have a mucotoxic effect. Recent advances have led to the use of radioimmunotherapy in patients with advanced NHL; Yttrium 90 ibritumomab tiuxetan has lower mucosal toxicity than standard chemotherapy.[31]

Mucositis during transplantation

The factors associated with the development of mucositis during autologous SCT are the amount of chemotherapy administered, the previous exposure to some drugs (e.g. anthracyclines, vinca alkaloids, cyclophosphamide, fludarabine, platinum analogs and methotrexate), female gender and the type of disease.[7] Furthermore, radiotherapy, a diagnosis of NHL and etoposide administration as part of the stem cell mobilizing regimen have been associated with worse mucositis.[32,33] Patients affected by hematologic malignancies have a higher risk of developing mucositis than those affected by solid tumors who are submitted to the same procedure.[34] Conditioning regimens, above all those containing busulfan and melphalan or based on radiotherapy, play a crucial role in the development of mucositis.

The BEAM schedule (BCNU, etoposide, cytarabine and melphalan) is currently used as a conditioning regimen for patients affected by lymphoma and is responsible for severe mucositis in 75% of cases.[35] The association of idarubicin with busulfan for autologous SCT in AML patients caused profound mucosal derangement in 82% of patients.[36] High doses of melphalan (200 mg/m^2), given prior to autologous SCT for multiple myeloma, caused mucosal injury in about 35% of them;[37] intermediate doses (100 mg/m^2) significantly reduced the incidence of mucositis to 23%, as reported in a study including patients over 70 years old.[38] In the allogeneic SCT setting, the incidence of mucositis reaches 75 to 100%, depending on the type of disease and procedure and on the conditioning regimen;[7] moreover, true ulcerations in the mouth have been reported in 76% of cases.[39] Risk factors for mucosal damage in allogeneic SCT are a pre-transplant body mass index higher than 25 as well as the use of total body irradiation (TBI) as part of the conditioning regimen.[40] Moreover MTX as prophylaxis for GVHD has been associated with a significantly higher incidence of mucositis than other immunosuppressive drugs.[41] Reduced myeloablative regimens for allogeneic SCT result in a low incidence of gastrointestinal toxicity.[42] GVHD can affect the whole gastrointestinal tract, the mouth being involved in 80% of the cases.[43,44]

Pain related to mucositis

The issue of pain related to mucositis has been poorly

Table 1. Pathobiological phases of mucositis.[2,7]

Biological phase	*Description and comments*
Phase 1: Initiation	RT or CT causes damage to the DNA in basal epithelial cells and generates ROS, which further damage cells and blood vessels in the submucosa.
Phase 2: Signaling	RT or CT and ROS induce apoptosis and upregulate inflammatory cytokines in cells.
Phase 3: Amplification	Inflammatory cytokines produce further tissue damage, amplifying signaling cascades and the injury process.
Phase 4: Ulceration	Loss of mucosal integrity produces extremely painful lesions, providing portals of entry for bacteria, viruses, and fungi.
Phase 5: Healing	Proliferation, differentiation, and migration of epithelial cells to restore the integrity of the mucosa. The presence of mucositis is associated with a decreased absolute neutrophil count (ANC), given that neutrophils and mucosal basal cells are actively reproducing cells that tend to be damaged by chemotherapeutic agents. They recover in parallel. Although healing of mucosal tissue is not dependent on the return of the ANC, the lesions tend to resolve when the ANC returns to normal, indicating normal mitotic activity of basal cells.

RT: radiotherapy; CT: chemotherapy; ROS: reactive oxygen species.

Table 2. Comparison between mucositis due to chemotherapy and GVHD.

	Pathogenesis	*Clinical features*	*Treatment*
Acute GVHD	LPS-mediated production of TNFα, IL-1, IL-12 (mediators of GVHD); chemotherapy and TBI cause inflammation; inflammation and LPS activate alloreactive donor T lymphocytes; 3-phase process	Associated with skin and liver damage. Begins some weeks after stem cell infusion	KGF for phase I; mycophenolate, tacrolimus, rapamycin, cyclosporine, anti CD40L for phase II; daclizumab, infliximab and antifungal therapy for phase III; pain control
Chemotherapy	5-phase process (Table 1)	Associated with granulocytopenia	KGF and derivatives; ongoing trials with other drugs (repifermin, AES-14); pain control
Chronic GVHD	Autoimmune disease due to aberrant thymic education of T-cell precursors	Resembles skin, ocular and salivary autoimmune diseases; intestinal strictures	mycophenolate, monoclonal antibodies (daclizumab, alemtuzumab, rituximab), sirolimus, pentostatin and extracorporeal photopheresis

addressed and almost exclusively in nursing literature. The incidence of oral mucositis-related pain syndromes is 40-70% among patients treated with chemotherapy, 100% in those in whom radiotherapy is delivered to treat head and neck tumors, and 60-85% in the setting of allogeneic SCT[45,46] with significant pain lasting from the 4th to the 11th day after transplantation.[39]

Pathogenesis

Typically, oral symptoms develop 5 to 8 days after the administration of chemotherapy and last approximately 7 to 14 days. OM was previously thought to be a four-phase biological process involving an inflammatory/vascular phase, an epithelial phase, an ulcerative/bacterial phase and a healing phase. The pathobiology of mucositis, including the gastrointestinal forms, is currently defined as a five-phase process: initiation, signaling with generation of messengers, amplification, ulceration, and, finally, healing (Table 1). Although this model is described in a linear way, injury occurs quickly and simultaneously in all mucosal tissues.[2] At the beginning DNA damage, generation of reactive oxygen species (ROS), and the coincident activation of other pathways occur. During the upregulation and message generation phase, transcription factors, such as nuclear factor κ-B (*NFκ-B*)[47] are activated to upregulate genes in the endothelium, fibroblasts, macrophages, and epithelium; this process is followed by the production of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin-1 β (IL-1β), interleukin-6 (IL-6), and enzymes, which mediate a series of biological events leading to apoptosis and amplification of the injury, loss of epithelial integrity and the development of ulceration.[2] At this stage, bacteria colonize the ulcer's surface and increase the injury by shedding of cell-wall products and, in the presence of granulocytopenia, may cause bacteremia and sepsis. Ultimately, spontaneous healing occurs.

The lesions in the mouth mainly involve the non-keratinised part that becomes susceptible to overinfection, while the cytopathic effect is more severe in the ileum. In a longitudinal study including patients who underwent myelosuppression and allogeneic SCT, oral ulcers were present in 76%, mostly affecting the non-keratinised mucosa, an average of 5 days after the infusion of the stem cells. The ulcers persisted for an average of 6 days and 90% of them had improved by day 15,[39] when the granulocyte count exceeded 500/mm^3.

GIM develops through multiple mechanisms including induction of crypt cell death (apoptosis) and cytostasis. Although the molecular control of these events throughout the gastrointestinal tract has yet to be fully elucidated, p53, of the Bcl-2 family, and caspases have been reported to be involved.[48] An increase of apoptosis can be observed by 24 hours after the administration of antiproliferative therapy, which is followed by a reduction in the length of the intestinal villi causing mucosal flattening around the 3rd day. From the 5th day, hyperplasia of the intestinal mucosa leads to the *ad integrum* recovery of the

Table 3. Comparison of oral mucositis assessment scales.[7,58]

Grade	*0*	*1*	*2*	*3*	*4*
WHO	None	Soreness ±erythema	Erythema, ulcers, and patient can swallow solid food	Ulcers with extensive erythema and patient cannot swallow solid food	Mucositis to the extent that alimentation is not possible
RTOG	None	Erythema of the mucosa	Patchy reaction <1.5 cm, non-contiguous	Confluent reaction >1.5 cm, contiguous	Necrosis or deep ulceration, ± bleeding
WCCNR	Lesions: none Color: pink Bleeding: none	Lesions: 1-4 Color: slight red Bleeding: N/A	Lesions: >4 Color: moderate red Bleeding: spontaneous	Lesions: coalescing Color: very red Bleeding: spontaneous	NA

Adapted from the WHO, RTOG, and WCCNR scales. WHO: World Health; Organization; RTOG: Radiation Therapy Oncology Group; WCCNR: Western Consortium for Cancer Nursing Research. NA: not applicable.

gastrointestinal barrier.[49] Although it is possible to assess gut mucosal damage by both sugar permeability tests and serum citrulline, these functional tests remain abnormal despite clinical resolution and full anatomic and functional recovery of the affected portions of the intestine.[50] The reason for this is not known.

Clinical features

The main symptom of OM is dysphagia, which may be mild or severe, together with nausea, sialorrhea, sometimes profuse, and infections. The pain syndromes can range from a sense of burning in the initial phases up to severe forms and are caused by a mixture of different types of pain. The main components are nociceptive pain, mediated by C fibers and relievable by opioids, and incidental pain, caused by movement and contact with the mucosal surface, mediated by the fast-conducting A-δ fibers. The latter component is insensitive to analgesics and the only effective pain treatment is the functional exclusion of the anatomic parts involved until the resolution of the ulcers and full recovery of the mouth's functionality. The symptoms of GIM are visceral pain (ranging from mild pain to projected abdominal wall pain), hypermotility with diarrhea, starting from the 3rd day after the beginning of the treatment and resolving by the 7th day, coinciding with the full clinical flare of the OM. In patients undergoing treatment including high doses of cytarabine, the diarrhea generally develops between the 5th and 8th day after starting chemotherapy and persists over the second week. This clinical picture is usually transitory after chemotherapy, while in some patients treated with radiotherapy the mucosal damage may evolve towards a chronic phase characterized by impaired absorption and altered intestinal motility. In addition, GIM can be complicated by gastrointestinal obstruction, perforation, and infection.[51]

Mucositis due to GVHD

The clinical manifestations of acute GVHD may be superimposed on those of cytotoxic GIM (Table 2). In a prospective study based on endoscopic evaluation and biopsy of the bowel of patients undergoing allogeneic SCT, the most frequent finding among symptomatic patients complaining of diarrhea was GIM[52,53] while only a minority of the patients were affected by GVHD.

The pathogenesis of acute GVHD is somewhat complex. Endotoxins, lipopolysaccharides (LPS) and intestinal flora all play important roles. LPS stimulate the production of TNF-α, IL-1 and IL-12, which are the mediators of GVHD. Moreover, inflammation and/or LPS may activate alloreactive donor T lymphocytes.[54,55] On the other hand, high dose chemotherapy and TBI, by causing the release of large quantities of inflammatory cytokines from the damaged agstrointestinal tract, contribute to the worsen-

Table 4. The OMI (Oral Mucositis Index).[59]

	LM		BM		Tongue			Floor of mouth	Soft palate
	Lower	Upper	Right	Left	Dorsal	Lateral	Ventral		
Atrophy									
Erythema									
Edema									
U/P									

Each box must have a number: Dorsal tongue atrophy: from normal length of filiform papilla to grade 3 (total loss of normal architecture) (0: normal; 1: mild atrophy; 2: moderate atrophy; 3= severe atrophy) Erythema: from normal redness to grade 3 (0: normal; 1: mild erythema; 2: moderate erythema; 3: severe erythema); Lateral tongue edema: from a normal to indented tongue (0: normal; = mild edema; 2: moderate edema; 3: severe edema). U/P: Ulcerations/pseudomemebrane: surface area of involvement for each site (0: normal; 1: ≥0 cm^2 but <1 cm^2; 2: ≥1cm^2 but < 2 cm^2; 3: ≥2cm^2).

Table 5. The Oral Mucositis Assessment Scale (OMAS) system.[6]

Erythema	
0	None (no change in the color of the mucosa)
1	mild/moderate (increase in the intensity of the color of the mucosa)
2	severe (mucosa the color of fresh blood)
Ulceration/pseudomembrane formation	
0	no lesions
1	cumulative surface area of lesion(s) in a single site less than 1 cm^2
2	cumulative surface area of lesion(s) in a single site greater than or equal to 1 $cm^2$and less than or equal to 3 cm^2
3	cumulative surface area of lesion(s) in a single site greater than 3 cm^2

The value of OMAS at any given assessment is obtained by summing the erythema and ulceration/pseudomembrane subscores at each site (possible score range, 0 to 5), and then averaging these scores across all sites (i.e. the maxillary labial mucosa, the mandibular labial mucosa, the right buccal mucosa, the left buccal mucosa, the right lateral and ventral tongue, the left lateral and ventral tongue, the floor of the mouth and lingual frenum, and the soft palate and fauces).

Table 6. NCI/CTC criteria for diarrhea.

Grade 1	Increase of less than four stools per day during pre-treatment
Grade 2	Increase of four to six stools per day or nocturnal stools
Grade 3	Increase of seven or more stools per day, or incontinence, or need for parenteral support for dehydration
Grade 4	Requiring intensive care or hemodynamic collapse

ing of GVHD.[54,56] Chronic GVHD rarely appears before day 80 after allogeneic SCT and oral involvement can be revealed by the following clinical findings: angular cheilitis, xerostomia, atrophy of the papillae, lichen planus and painful ulcers on the sides of the tongue. In addition, involvement of the salivary glands, with consequences ranging from transient xerostomia to complete destruction of the glandular structures, has also been reported.[55] Lastly, the involvement of the gastrointestinal tract by chronic GVHD is characterized by abnormal motility and bowel strictures and stenosis, sometimes requiring surgical treatment.

Diagnostic criteria and clinical evaluation

The assessment and clinical evaluation of mucositis still pose challenges in clinical practice due to the lack of standard diagnostic criteria established by controlled studies.[7] Briefly, the World Health Organization (WHO) Oral Toxicity Scale measures anatomical, symptomatic, and functional components of OM. The severity of the condition is graded by a scale from 0 (no oral mucositis) to 4 (patient requiring TPN). By contrast, the Radiation Therapy Oncology Group (RTOG), Acute Radiation Morbidity Scoring Criteria for mucous membranes, and the revised OM staging system of the Western Consortium for Cancer Nursing Research (WCCNR), assess only the anatomical changes associated with OM. The WCCNR scale is a 4-grade assessment tool (Table 3).[7,58]

The Oral Mucositis Index (OMI) considers the severity of OM in terms of erythema, ulceration, atrophy and edema (Table 4), each graded on a scale from 0 to 3 (0=none, 3=severe). The OMI has been shown to be internally consistent with high test-retest and inter-rater reliability and exhibits strong evidence of construct validity.[59]

The Oral Mucositis Assessment Scale (OMAS) has been proven to be highly reproducible between observers and accurate in recording elements associated with OM. The OMAS (Table 5) provides an objective assessment of OM and is also a significant predictor of important outcomes in transplanted patients. The score estimates the presence and size of ulcerations or pseudomembranes (score 0 to 3; 0=no lesion; 1=lesion <1cm^2; 2= lesion of 1cm^2 to 3cm^2; 3= lesion > 3cm^2) and erythema (score 0 to 2; 0=none; 1=not severe; 2=severe) on the upper and lower lips, right and left cheeks, right and left ventral and lateral tongue, floor of the mouth, soft palate/fauces and hard palate.[6,7]

The evaluation of GIM relies on the presence and the frequency of signs and/or symptoms, diarrhea (volume and frequency of the evacuations) and the onset of complications. The principal instruments used to assess GIM have been described by Sonis *et al.*[7] Table 6 presents the NCI/CTC criteria for grading mucositis-associated diarrhea. A critical aspect in the management of these patients, particularly those with OM, is the regular assessment of the pain.[60] Various assessment tools are described elsewhere.[3,61]

Prevention of mucositis

Despite its clinical significance, there is still no standard approach to the prevention or treatment of mucositis. Interventions have been limited to the use of palliative measures, barrier protectants, topical antimicrobials, ice, and analgesics, although none of these measures has proven to be consistently effective.[62] Basic oral hygiene, periodic control of dental health and comprehensive patient education are important components of the care of any patient with hematologic malignancies at risk of OM.[63]

Effective approaches for the prevention and management of OM include oral cryotherapy and low-level laser therapy for patients undergoing SCT.[64] Cryotherapy seems to be effective in limited areas of the oral mucosa, as well as a treatment for melphalan-induced mucositis.[65] Antibiotic prophylaxis, although considered a reasonable measure in subjects undergoing myelosuppression, is ineffective in reducing the colonizing microbes present on the mucosal surface during autologous SCT.[66] The topical application of chlorhexidine,[67] GM-CSF,[67] the salivary production stimulator pilocarpine,[68] and histamine gel[69] is not recommended for the prophylaxis of OM given the reported lack of efficacyof these agents. Moreover, no benefits have been found from the use of the amino acid glutamine in the setting of SCT.[70]

Benzydamine, a molecule exerting antioxidant and anti-inflammatory effects by decreasing TNF-α, IL-1β and

Table 7. Growth factors and cytokines to treat or prevent mucositis.[78]

	Activity	*Effects*
Palifermin	Mitogenic for fibroblasts, keratinocytes, endothelial cells, increases mucosal thickness, upregulates Bcl-2, detoxifies ROS, attenuates effects of TNF-α and the expression of adhesion molecules	Significantly reduced both the incidence and duration of grade 3-4 OM after myeloablative therapy
Repifermin (FGF-10)	Selective epithelial cell proliferation	Seems active in reducing OM in SCT
Velafermin (FGF-20)	Mesenchymal and epithelial cell proliferation	Phase I ongoing
Epidermal growth factor (EGF)	Proliferation and differentiation of various tissues	Role unknown for OM. No trial from 2002
GM-CSF	Development of granulocyte-monocyte cell lines	No positive effects on mucositis
Transforming growth factor (TGF)-β3	Arrests epithelial cells in G1 phase	No beneficial effects
Whey-derived growth factor extract (WGFE)	Bovine derivative containing FGF, TGF, IGF, PDGF	No beneficial effects in hamsters
Glucagon-like peptide-2 (GLP-2)	Influences proliferation in crypt cells	Some positive effect in animals
Lactoferrin	Regulates inflammation, activity against infection	Some positive effect in rats
RDP-58	Inhibits production of TNF-α, IL-12 and IFN-γ	Reduced diarrhea and mucosal inflammation in mice
rhIL-11	Activates megakaryocytopoiesis, down-regulates inflammatory cytokines	No results in SCT, serious side-effects
Insulin-like growth factor (IGF-I)	Enhances mucosal repair	Partially active in rats

prostaglandin synthesis, and by inhibiting leukocyte-endothelial interactions, has been shown to exert analgesic effects in patients at risk of OM;[71] the antibiotic clarithromycin,[72] which stimulates macrophage functions, has also shown a partial effectiveness. Amifostine, a cytoprotectant free radical scavenger, has been successfully employed in the prevention of mucositis following SCT,[73] while the potential role of non-steroidal anti-inflammatory drugs, although promising, has not yet been established.[74] Therefore, to date, none of the above described agents has been recognized or recommended as the gold standard for the prophylaxis and/or the treatment of mucositis. A consensus has recently been reached on the use of sulfalazine to prevent gastrointestinal mucositis in patients undergoing radiotherapy, while octreotide is considered useful for reducing the frequency and volume of diarrhea.[62]

Table 8. Regulation and monitoring of variables involved in patient-controlled anesthesia.

Variables	*Setting and regulation*
Loading dose	The effective starting dose allowing complete relief or, at least, significant alleviation of pain (i.e. IV morphine 1 mg/5 minutes until pain relief).
Incremental dose	The dose deliverable by the device system in response to the patient's demand (IV morphine 0.5 – 1.0 mg).
Duration	Time to deliver the incremental dose (usually, at least 5 minutes for IV morphine).
Lock-out time	The controlled time between two consecutive incremental doses (IV morphine 5–15 minutes).
Background infusion	Basal opioid infusion. Usually not required.
Concentration	Constant and carefully monitoring of the concentration of analgesic solutions is needed.
Hourly or fourthly limits	Pre-established amount of opioid that the patient may periodically require. Caution and safety limits adopted to avoid opioid over dosage.

IV: intravenous.

Treatment of mucositis

In recent years, considerable research has been conducted on the pathobiology of mucositis in search for novel therapeutic agents.[75] Among the latest discoveries, the most promising is palifermin, a human recombinant keratinocyte growth factor (KGF).[76] Upon activation of the transcription factor Nrf2, which encodes for other genes playing a role in detoxifying ROS, palifermin exerts its effects on keratinocytes, fibroblasts and endothelial cells. Moreover, KGF has the ability to attenuate the effects of TNF-α and the expression of adhesion molecules. In a clinical trial this drug, compared to a placebo, significantly reduced the incidence and duration of severe OM (WHO grade 3-4) after myeloablative therapy in cancer patients.[76]

Therefore, palifermin and two human fibroblast growth factors (repifermin, velafermin)[77] could pave the road to a targeted approach to the prevention of mucositis.[78,79] Some compounds under evaluation for the treatment or prevention of mucositis are listed in Table 7.

Approach to GVHD-related mucositis

The current therapeutic approach to GVHD-induced mucositis exploits agents thought to be capable of interfering with the pathogenesis of the disease. KGF may be useful for lowering levels of LPS and TNF-α,[80] while cyclosporine, mycophenolate, tacrolimus, anti-CD40 ligand antibodies and sirolimus (rapamycin) block donor T-cell activation and differentiation.[81] Furthermore, daclizumab (IL-2 receptor antagonist) or infliximab (anti-TNF-α antibody), coupled with antifungal therapy, are

effective against cytotoxicity towards the host target.[82] The topical treatment of oral ulcers due to acute GVHD includes steroids[83] and tacrolimus.[84] In contrast, steroids are not first-line treatment for chronic GVHD, since new immunomodulators such as mycophenolate, monoclonal antibodies (daclizumab, alemtuzumab, and rituximab), sirolimus and pentostatin are more effective and lack the long-term side-effects of steroids.[85]

Supportive therapy and pain control

Supportive therapy and control of symptoms are critical aspects of the management of patients with mucositis, who generally receive TPN and analgesics. Recently, the role of TPN required for less than 10 days for OM in pediatric patients has been discussed. In a prospective randomized study, 30 children with WHO grade 4 OM were assigned to receive either TPN or intravenous fluid therapy. No differences in recovery of peripheral white blood cells, incidence of infections, hospitalization time, days on intravenous antibiotics, days on opioid analgesics or delay of the next scheduled chemotherapy course were observed between the two groups.[86]

Analgesic therapy is an essential measure that, besides relieving pain, can allow the resumption of oral alimentation and reduce the time spent in hospital.[87] However, the only measure to control the incidental pain related to mastication and swallowing is to exclude oral feeding and institute TPN or intravenous fluid therapy. Topical analgesics and anesthetics have been proposed to be of potential use in controlling the nociceptive pain component.[88] Nevertheless, the mainstay of analgesic therapy in patients with OM is parenteral administration of opioids: tramadol can be employed for the control of mild to moderate pain,[61] while intravenous morphine is the recommended fisrt-line therapy to relieve more severe pain. This can be administered using a system of patient-controlled analgesia (PCA), which is associated with lower doses and a shorter duration of opioid therapy, when compared with a continuous infusion system,[89] although requiring careful monitoring by skilled nurses. Table 8 shows the main parameters to be considered for the use of PCA. Little experience exists on the use of transdermal buprenorphine in the setting of SCT, while conflicting results have been reported on the efficacy of transdermal fentanyl as a pain reliever in patients undergoing autologous SCT.[90-92]

Conclusions

Our understanding of the biological basis of mucosal barrier injury induced by antitumor therapies continues to evolve, opening the promising perspective of a possible pathogenetic-based approach to the prophylaxis and treatment of mucositis. The mucosal response to cytotoxic insults appears to be controlled by both global factors (gender, underlying systemic disease and race) and tissue-specific factors (epithelial type, local microbial environment and function). Interactions between these elements, coupled with underlying genetic influences, most likely govern the risk, course and severity of regimen-related mucosal injury.[93] Further progress in the field of pharmacogenomics may allow treatment to be tailored according to the enzymatic profile of the individual patient to attain a more favorable balance between the clinical benefit and side effects of cytostatic chemotherapy whilst obviating the need for dose reductions.

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