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Adverse Event Management of Oral Mucositis in Patients with Breast Cancer

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Keywords

Oral mucositis · Disease management · Breast cancer · Chemotherapy · Molecular targeted therapy

Summary

Oral mucositis (OM) is a clinically important and frequent adverse event (AE) associated with cancer treatment with conventional chemotherapy as well as new targeted agents. Incidence and severity of OM vary from treatment to treatment and from patient to patient. The pathogenesis of chemotherapy-induced OM can be divided into 5 phases. OM induced by targeted therapies differs among other things in appearance, course, concomitant AEs and toxicity, and thus could be perceived as an entity distinct from chemotherapy-induced OM with an innate pathogenic mechanism. OM has a severe impact on a patient's quality of life (QoL) by causing complications such as pain and discomfort. Even more important are associated restrictions in nutrition and hydration. Thus, the efficacy of cancer therapy might be impaired due to the necessity of dose delays and dose reductions. Numerous preventive and therapeutic approaches have been evaluated, but currently no single agent has changed the standard of care in preventing and treating OM. Thus, the current management has evolved from clinical experience rather than clinical evidence. This article will review the AE 'OM' induced by breast cancer treatment with chemotherapy and targeted agents in order to provide practical guidance for management and prevention.

Introduction

Oral mucositis (OM) is a common and often dose-limiting adverse event (AE) of cancer therapy with the potential to cause severe sequelae and have a strong impact on a patient's quality of life (QoL), health care costs, and ultimately outcome by influencing the treatment dose [1]. OM can be observed in patients with breast cancer treated with conventional chemotherapeutic drugs as well as in patients receiving targeted therapies such as the tyrosine kinase inhibitor (TKI) lapatinib and the mammalian target of rapamycin (mTOR) inhibitor everolimus [2–4]. Radiotherapy-induced OM is not a problem in breast cancer patients. In principle, OM is initiated by an inflammatory process affecting the mucosa of the oral cavity or other areas of the gastrointestinal tract. The lesions can sometimes be large in size and are often associated with intense pain which can compromise nutrition and oral hygiene [5, 6]. In addition, there is an increased risk for local and systemic infections due to treatment-induced compromised immunity and damaged oral mucosa [7]. Thus, accurate diagnosis of OM and prompt initiation of prophylaxis and treatment are mandatory.

Pathogenesis of Mucositis

Understanding the pathogenesis of mucositis is the key to effective treatment and prevention. Recent studies have indicated that the mechanisms that result in mucositis are complex. Cytotoxic treatment affects the epithelium as well as all other tissues and cells of the mucosa. The model of the pathogenesis of mucositis developed by Sonis et al. [5] suggests a process divided into 5 phases: initiation, upregulation with generation of messenger signals, signalling and amplification, ulceration, and healing. To date, it is unproven whether the

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Table 1. Risk of NCI-CTC grade 3–4 oral mucositis with frequently used chemotherapeutic regimens (modified from [12])

Regimen	Grade 3–4 risk, %
All breast	4.08
A→T→C: doxorubicin, taxane[a], and cyclophosphamide (administered sequentially)	2.29
AC→T: doxorubicin, cyclophosphamide, and taxane[a] (administered sequentially)	2.80
A→CT: doxorubicin, cyclophosphamide, and taxane[a] (administered sequentially)	5.26
A→T: doxorubicin and taxane[a] (administered sequentially)	4.17
AT: doxorubicin and taxane[a]	8.33
FAC (weekly): 5-FU, doxorubicin, and cyclophosphamide	3.33
AC (weekly): doxorubicin and cyclophosphamide	13.64
Paclitaxel (weekly)	2.87
TAC: docetaxel, doxorubicin, and cyclophosphamide	4.92

[a]Paclitaxel or docetaxel.
5-FU = 5-Fluorouracil.

pathogenesis of mucositis observed in patients receiving new molecular targeted therapies is comparable with that of mucositis caused by conventional cancer therapies and radiation [8]. OM caused by targeted therapies differs among other things in appearance, course, concomitant AEs and toxicity, and thus could be perceived as an entity distinct from conventional OM with its own pathogenic mechanisms. Some authors strongly believe that immune mechanisms are involved in this process, but further research is needed [9, 10].

Incidence and Risk Factors for Oral Mucositis

Unfortunately, there is overall wide variability and no reliable way of predicting which patients will develop OM. The severity and incidence of OM in patients with breast cancer depend on a number of specific factors such as the underlying systemic disease, type of treatment, dosage and frequency of chemotherapeutic agents, and patient-related risk factors [11]. Several standard chemotherapeutic agents such as 5-fluorouracil (5-FU), anthracyclines and taxanes are known to be associated with high rates of OM [12] (table 1). For the treatment of hormone receptor-positive, HER2-negative metastatic breast cancer (MBC), the mTOR inhibitor everolimus in combination with exemestane is one standard treatment. As shown in the phase III BOLERO-2 study of everolimus and exemestane, the incidence as well as the severity of AEs were comparable with everolimus monotherapy. 56% of the patients developed OM of any grade, of which 48% experienced mild to moderate grade 1–2 OM, and 8% grade 3–4 OM according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale version 3, 0 [13, 14]. Recent reviews indicated that with an incidence of 44%, OM is the most common treatment-related AE associated with everolimus [9, 15]. Lapatinib is a dual TKI that reversibly inhibits the tyrosine kinase domain of ErbB1 (EGFR) and ErbB2 (HER2) receptor intracellularly. Lapatinib is approved for the treatment of HER2-overexpressing MBC in combination with capecitabine, trastuzumab, or an aromatase inhibitor. Only when used in combination with capecitabine, OM is a frequently reported AE [2, 16], whereas other TKIs such as sunitinib and sorafenib, used for example in the treatment of advanced renal cell carcinoma, can cause OM also as monotherapy [3, 17]. Among patient-related risk factors, age [18, 19], gender [20], and comorbidities such as malnutrition and poor oral health can contribute relevantly to the risk of OM [11, 21].

Clinical Manifestation and Diagnosis of Oral Mucositis

Diagnosis of OM caused by cancer treatment is usually based on clinical presentation, location, as well as onset and course of these lesions. The initial signs and symptoms of OM induced by conventional chemotherapeutic agents are typically a painful erythema of the oral mucosa starting within the first week of chemotherapy, followed by erosions and irregular ulceration with a white pseudomembrane. The lesions are typically located on the unkeratinised movable mucosa, may increase in size, and are associated with intense pain which can compromise swallowing, talking, and finally also nutrition and oral hygiene [6, 7]. The damage to the oral mucosa leads to an impaired barrier function resulting in an increased risk for local as well as systemic infections. After chemotherapy, the healing process of OM takes approximately 2–4 weeks, and recovery is without sequelae [1].

In contrast to ulcerations caused by conventional chemotherapeutic agents or radiotherapy, the clinical manifestation of oral lesions in patients receiving the mTOR inhibitor everolimus is characterized by an inflammatory process with well-demarcated, ovoid, aphthous-like ulcers with a grey area surrounded by an erythematous halo. In addition, they tend to be smaller, more discrete, and less widespread. Usually, the lesions are also located on the unkeratinised mucosa, especially on the side of the tongue, the buccal mucosa, the inside of the lips, and the soft palate [9, 22–24]. Even though the clinical presentation of these lesions seems to be of mild or

Table 2. Comparison of selected assessment scales

Scale	WHO Oral Toxicity Scale [28]	NCI-CTCAE v 3, 0 [14]		NCI-CTCAE v 4, 0 [29]
Description	developed for OM due to CT, RT and HSCT; scale combines objective mucosal changes with subjective parameters and functional outcomes	developed for AEs associated with CT, RT and HSCT; 2 different AEs combine objective mucosal changes (clinical exam) and subjective and functional parameters (functional/ symptomatic)		developed for AEs associated with CT, RT and HSCT. Scale combines subjective and functional parameters.
Name of AE	–	mucositis: clinical exam	mucositis: functional/symptomatic	OM
Grade 0	none	–	–	–
Grade 1	oral soreness, erythema	erythema of the mucosa	UAT: minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function GIS: minimal discomfort, intervention not indicated	asymptomatic or mild symptoms; intervention not indicated
Grade 2	oral erythema, ulcers, can eat solids	patchy ulcerations or pseudomembranes	UAT: symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL GIS: symptomatic, medical intervention indicated but not interfering with ADL	moderate pain; not interfering with oral intake, modified diet indicated
Grade 3	oral ulcers, liquid diet only	confluent ulcerations or pseudomembranes; bleeding with minor trauma	UAT: symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL GIS: stool incontinence or other symptoms interfering with ADL	severe pain; interfering with oral intake
Grade 4	oral alimentation not possible	tissue necrosis; significant spontaneous bleeding; life-threatening consequences	symptoms with life-threatening consequences	life-threatening consequences; urgent intervention indicated
Grade 5	–	death	death	death
OM due to mTOR inhibitors/TKIs [9, 25]	risk for underscoring	suitable		high risk for underscoring

AE = Adverse event; ADL = activities of daily living; CT = chemotherapy; HSCT = hematopoietic stem cell transplantation; RT = radiotherapy; UAT = upper aerodigestive tract sites; GIS = lower gastrointestinal sites; OM = oral mucositis.

moderate severity, they are often associated with intense pain and dysphagia [25]. In general, mTOR-associated OM resembles more the appearance of aphthous stomatitis. It is of special interest that in contrast to OM triggered by conventional chemotherapy, patients are sometimes affected by these painful and unpleasant clinical symptoms in the absence of any apparent clinical signs. It is noteworthy that OM due to targeted therapy with mTOR inhibitors starts soon after treatment initiation and is self-limiting in most cases [9, 25]. In the BOLERO-2 study, more than a third of the oral events (grade ≥ 2) were reported within the first 2 weeks after initiation of treatment with everolimus and exemestane, and in the further course of the study oral events began to plateau at 6 weeks [10]. Furthermore, common infectious diseases like oral candidiasis and herpes simplex virus are also frequently seen in cancer patients receiving chemotherapy and can have a clinical appearance similar to OM; thus, they should be considered in the differential diagnosis [26].

Assessment Scales

Exact documentation and classification of OM is crucial for any dose modifications of the given cancer treatment. Therefore, a number of clinical assessment and grading tools have been evaluated and reported [5, 27]. The scales differ widely in content and complexity; thus, the selection of a specific scale should depend on the reason for grading a specific case of OM. 2 of the most common scales used in research and clinical care settings are the World Health Organization

(WHO) oral toxicity scale and the NCI-CTCAE system [14, 28, 29]. These scales have been developed for assessing OM induced by conventional chemotherapy, hematopoietic stem cell transplantation, and radiotherapy, and they provide objective, subjective, and functional parameters. Unfortunately, there is currently no validated grading scale for OM due to targeted therapy. As outlined above, patients receiving new targeted therapies sometimes present with clinical symptoms of oral burden but no clinically apparent signs, or inconspicuous but very painful lesions. Consequently, the WHO as well as the NCI-CTCAE scales have several limitations concerning the assessment of targeted therapy-associated oral AEs and may underestimate the morbidity of these oral lesions and the severe impact of treatment-related OM on patients' QoL (table 2). Therefore, the development of new specific scales such as the Patient-Reported Oral Mucositis Symptom (PROMS) scale is warranted. The PROMS scale was assessed by Gussgard et al. [30] in patients with head and neck cancer, and may be a feasible substitute for clinician-based scoring tools to quantify OM experienced by patients. This may lead to enhanced assessment of OM.

Prevention and Treatment Options for Oral Mucositis due to Breast Cancer Therapy

Although a great number of therapeutic options have been developed and evaluated in recent years, research remains scanty and thus proven preventative and treatment approaches to help reduce the severity of OM are still limited. Existing agents differ widely in their mode of action, e.g. oral decontamination, stimulation of oral epithelial cell proliferation, and protection by coating the oral mucosa, and current management of OM has mostly evolved from clinical experience rather than clinical evidence. To standardize prevention and management of OM caused by chemotherapy and/or radiation therapy, the Clinical Practice Guidelines for Mucositis were created by a comprehensive review of the related literature by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) in partnership with the International Society of Oral Oncology (ISOO) [21]. The second update of these guidelines has recently been published [31]. In addition, further recommendations and management strategies for OM have been established by different organisations such as the National Comprehensive Cancer Network (NCCN) who published a multidisciplinary task force report on the key issues of OM [32] or the European Society for Medical Oncology (ESMO) with their clinical practice guidelines [11]. In contrast, clinical management of mTOR inhibitor- and TKI-associated oral complications is mainly based on expert opinion and similar to management options for the prevention and treatment of OM induced by chemotherapy agents as well as of conventional aphthous stomatitis [25]. The subsequent sections summarise the recommended main strategies and agents for OM induced by breast cancer therapy to provide practical guidance concerning the management of OM.

Patient Education and Basic Oral Care

All patients regardless of age and type of cancer therapy as well as caregivers and family members should be well informed about the risk of OM as a possible consequence of the planned therapy. Proper education on the importance of optimal oral hygiene including careful brushing with a soft bristle toothbrush, flossing, and non-medicated alcohol-free mouth rinses with e.g. saline or sodium bicarbonate several times a day are key elements [4, 12, 21, 33]. Mouth washes with peroxide, iodine, and thyme derivatives can worsen the OM and should be avoided during cancer therapy with everolimus [34]. Due to its antiplaque and antimicrobial effects, chlorhexidine may be considered as part of basic oral care [35]. Exogenous noxae such as tobacco, alcohol, and spicy, acidic or very hot food should be avoided during treatment [4, 25]. In addition, a dental examination before initiation and during cancer treatment is recommended as well as regular dental prophylaxis and treatment whenever indicated [21, 23, 35].

Pain Management and Nutritional Support

Pain assessment by validated instruments for self-reporting and pain management is an integral component of patient care due to the fact that mucositis is often associated with intense pain impacting nutrition, QOL, and treatment adherence. Painful symptoms and oral discomfort should be diagnosed in time and treated carefully. In addition to adequate individualized oral or systemic pain therapy in line with the guidelines of the WHO, there are various topical approaches to reduce pain [21]. Although there is no evidence for their efficacy in preventing or treating OM, widely used topical anaesthetic rinses with e.g. lidocaine or benzocaine as well as topically administered agents e.g. Gelclair® (DARA BioSchiences Inc., Raleigh, NC, USA), Caphosol® (EUSA Pharma, Oxford, UK), or 'magic mouthwashes' may provide pain relief for a short time and ameliorate oral discomfort [11, 22, 35, 36]. Concerning this matter, there are conflicting recommendations in particular for 'magic mouthwashes' which are non-standardized medical preparations with a mixture of ingredients prescribed for a specific purpose and to treat a variety of oral conditions. Variations in ingredients are common and may comprise topical anaesthetics, corticosteroids, antibiotics, or antifungals often in combination with diphenhydramine and/or an antacid to enhance the local anaesthetic effect or the adherence of the ingredients to the mucosa. The NCCN task force suggests the use of such mouthwashes [32], while they should be avoided according to the MASCC-ISOO

guidelines [21]. In any case, it is important to note that any undesirable side effects that may be associated with their use, e.g. suppression of the gag reflex and numbness by use of lidocaine [35], must constitute acceptable risks when weighed against the benefits to the patient. Pain and dysfunction due to OM can compromise alimentation and may result in malnutrition and inadequate hydration. Consequently, in addition to pain assessment, food intake and weight should be monitored. A soft diet and liquid diet supplements may be useful to improve chewing and swallowing. In the case of xerostomia, frequent sips of water, sugar-free chewing gum or candy, and artificial saliva are frequently used and may help to relieve symptoms in some patients [1, 25].

Prevention: Oral Cryotherapy and 5-FU-Based Chemotherapy

Several studies have demonstrated efficacy of cryotherapy in preventing OM in patients receiving bolus doses of 5-FU chemotherapy. Topical administration of ice cubes results in local vasoconstriction and reduced blood flow with subsequent lower cytotoxic effects on the cells of the oral mucosa [37]. Ice cubes are placed into the oral cavity 5 min before administration of bolus-dose 5-FU and should be left in the mouth for 30 min. Unfortunately, cryotherapy with ice cubes may not be well tolerated by some patients [38].

Specific Care of Moderate and Severe OM Induced by Everolimus

OM due to targeted therapies is not identical to OM caused by cytotoxic chemotherapies, and thus could be viewed as an entity distinct from conventional OM with its own mechanisms of pathogenesis. Mechanisms being considered include immune processes, and therefore anti-inflammatory agents as well as corticosteroids are promising approaches [9, 10]. In the case of severe OM, local, systemic, or intralesional corticoids are suggested for OM management. In the case of failure of all management options including the above, dose reductions or discontinuation of everolimus should be considered [8, 25, 34].

Treatment of Infections

Damage to the oral mucosa and reduced immunity due to cancer therapy make patients prone to opportunistic infections such as oral candidiasis and herpes simplex infection. Thus, all patients regardless of age and type of cancer therapy should be regularly evaluated for infections and treated with antiviral or antifungal medication whenever indicated. Attention should be paid to potential cytochrome P450-mediated interactions between systemically administered antifungal agents (such as fluconazole) and everolimus [34]. For this reason, topical antifungal medication with e.g. nystatin is preferable [3, 25].

New Approaches in the Treatment of Oral Mucositis

Based on the model for pathogenesis of mucositis [5] with complex biological inflammatory pathways, several potential therapeutic targets like growth factors (e.g. palifermine) [39], free radical scavengers (e.g. aminofostine) [40], anti-inflammatory agents (e.g. benzydamine hydrochloride) [41], cytokines [39], and glutamine [12] have been investigated for the treatment of OM. Another therapeutic approach is the use of the topical mucosal agent sucralfate due to its ability to bind to ulcerated mucous membranes [36]. However, up to now there is no proven benefit to support the use of any of these agents for the treatment of OM induced by breast cancer therapy with chemotherapeutic agents or TKIs and mTOR inhibitors.

Radiation at certain wavelengths has shown beneficial effects on tissues and cells, although the exact mechanism of action is not well understood. Several studies have indicated that the use of low-level laser therapy can ameliorate the symptoms and severity of chemotherapy-induced OM, and the evidence supported the development of 2 guidelines by the MASCC/ISOO in favour of low-level laser therapy for the prevention of OM in patients receiving high-dose chemotherapy with or without total body irritation before hematopoietic stem cell transplant and for patients undergoing radiotherapy due to head and neck cancer [31]. There are no data and therefore no specific recommendations for breast cancer patients and their underlying specific cancer treatments. Consequently, further well-designed research to evaluate the efficacy of laser und light therapies on OM in breast cancer patients should be performed [42].

Conclusion

The onset of OM is a common and sometimes dose-limiting side effect of several keystone treatments in solid cancers. In principle, OM can be divided into 2 different activation procedures based on the use of either classical cytotoxic drugs and radiation or new molecular targeted drugs such as the mTOR inhibitor everolimus, with implications on prevention and treatment options. It is mandatory to educate patients and their families and to council them thoroughly on first signs and symptoms of OM and the use and initiation of supportive care. Treatment of OM and dose reductions or interruptions of the underlying anti-cancer therapy ought to be carefully considered based on clinical manifestations and clinician-based assessments as well as the severity of OM experienced by the individual patient. Continued advances in the

understanding of the pathogenesis of OM and further development of more specific assessment tools and therapeutic approaches will lead to improved QoL and treatment for patients.

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