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SPECIAL ARTICLE

Systematic review of cytokines and growth factors for the management of oral mucositis in cancer patients

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Abstract
Purpose The aim of this project was to review the literature and define clinical practice guidelines for the use of cytokines and growth factor agents for the prevention or treatment of oral mucositis induced by cancer chemotherapy or radiotherapy.

Methods A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO). The body of evidence for each intervention, in each cancer treatment setting, was assigned an evidence level. Based on the evidence level, one of the

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following three guideline determinations was possible: Recommendation, Suggestion, No guideline possible.
Results Sixty-four clinical studies across 11 interventions were evaluated. A recommendation was made for the use of recombinant human KGF-1 (palifermin) at a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplant for prevention of oral mucositis in patients receiving high-dose chemotherapy and total body irradiation followed by autologous stem cell transplantation for hematological malignancies. A suggestion was made against using granulocyte macrophage colony-stimulating factor mouthwash for the prevention of oral mucositis in the setting of high-dose chemotherapy followed by autologous or allogeneic stem cell transplantation. No guideline was possible for any other cytokine or growth factor agents due to inconclusive evidence.
Conclusions Of the cytokine and growth factor agents studied for oral mucositis, the evidence only supports use of palifermin in the specific population listed above. Additional well-designed research is needed on other cytokine and growth factor interventions and in other cancer treatment settings.

Keywords Mucositis · Guidelines · Cytokines · Growth factors · Systematic review

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Introduction

Growth factors and cytokines bind to specific receptors on the cell membrane of target cells. Growth factors are proteins that stimulate cellular growth, proliferation, and differentiation. Cytokines are proteins or glycoproteins that modulate inflammatory and immune responses. There is evidence to suggest that pro-inflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha play an important role in the pathogenesis of mucositis [1].

Growth factors and anti-inflammatory cytokines may be useful in preventing chemotherapy (CT) and/or radiotherapy (RT)-induced mucositis. A number of such agents have been hypothesized to ameliorate the course of mucositis and are described below.

Keratinocyte growth factors (KGF) are members of the fibroblast growth factor (FGF) superfamily. Palifermin is a human recombinant keratinocyte growth factor (KGF-1 or FGF-7) that has pleiotropic activity. It is mitogenic for epithelial and endothelial cells, fibroblasts, and keratinocytes, thereby supporting barrier integrity [2]. Furthermore, KGF-1 is involved in a number of cell survival activities. These include upregulation of the expression of apoptosis regulator B-cell lymphoma-2, which suppresses apoptosis. KGF-1 also activates a redox-sensitive transcription factor, nerve growth factor-2 (Nrf2) that coordinates the expression of cytoprotective genes in cells including keratinocytes, endothelial cells, and fibroblasts. This results in the production of reactive oxygen species-detoxifying enzymes and a modulation of the cellular response to stress [3]. In addition, palifermin upregulates IL-13, an anti-inflammatory cytokine that attenuates the effects of TNF. Although speculative, KGF may downregulate other pro-inflammatory cytokines that are involved in the pathobiology of mucositis [4]. Animal studies suggest that KGF-1 decreases graft-versus-host disease (GVHD) associated with allogeneic hematopoietic stem cell transplantation (HSCT) [5, 6] and enhances T cell reconstitution [7]. Two other members of the KGF family, FGF-20 (velafermin) [8] and human recombinant KGF-2 (repifermin) [9], have overlapping activity with KGF-1 but may also have other actions that impact their effectiveness.

Colony-stimulating factors are specific hematopoietic growth factors needed for bone marrow progenitor cells to form mature blood cells. Granulocyte colony-stimulating factor (G-CSF) stimulates the development of neutrophils, eosinophils, and basophils, whereas granulocyte–macrophage colony-stimulating factor (GM-CSF) stimulates the generation of cells belonging to the monocyte/macrophage lineage. In addition, both G-CSF and GM-CSF enhance the function of peripheral neutrophils, including those in mucosal tissues. GM-CSF has activity on the proliferation of keratinocytes, and animal studies suggest that it enhances wound healing [10]. Direct actions of colony-stimulating

factors on peripheral cells as well as a temporal relationship of healing of mucositis and bone marrow recovery have been the rationale for numerous clinical studies testing G-CSF and GM-CSF for the prevention and treatment of oral mucositis.

Epidermal growth factor (EGF) is a polypeptide that plays an important role in maintaining tissue homeostasis as it regulates epithelial cell proliferation, growth, and migration. In addition, EGF enhances mucosal wound healing and tissue generation, suggesting that it may be effective in the treatment of ulcerative oral mucositis [11]. There is evidence to suggest that decreased salivary EGF is associated with more severe RT-induced mucositis [12, 13]. However, EGF and EGF-like peptides are overexpressed in the majority of human carcinomas and are likely involved in the pathogenesis of these tumors. Thus, concerns may be raised on a potential effect of topical EGF on tumor growth, particularly head and neck (H&N) carcinomas.

Transforming growth factor-beta (TGF-β) is part of the transforming growth factor-beta superfamily. TGF-β is a peptide that acts as an antiproliferative factor in many cell types, including epithelial cells and endothelial cells. TGF-β inhibits epithelial cell mitosis by arresting cells in the G1-phase and may thus have the potential to reduce mucositis [14].

Whey-derived growth factor extract contains biologically active proteins including TGF-β, FGF, insulin-like growth factor, and platelet-derived growth factor [15].

IL-11 is a pleiotropic cytokine that can be isolated from bone marrow-derived stromal cells. It is a key regulator of multiple events in hematopoiesis, most notably the stimulation of megakaryocyte maturation. In murine HSCT models, IL-11 reduces gut permeability, induces T helper-2 cell differentiation, and accelerates recovery of oral and bowel mucosa [16]. IL-11 also favorably modulated RT-induced oral mucositis in a hamster model by attenuating pro-inflammatory cytokine expression [17].

ATL-104 is a potent plant lectin mitogen for epithelial cells of the gastrointestinal tract. In an animal model, ATL-104 aids regeneration of CT-induced damage to the gastrointestinal tract [18].

The trefoil factor (TFF) family comprises a group of small growth factor-like peptides, which are highly expressed in tissues containing mucus-producing cells, particularly the mucosa lining the gastrointestinal tract. Although not a growth factor per se, TFF plays a role in maintaining mucosal integrity and repairing damaged mucosa and was therefore included in this review. In vitro studies have shown that TFF peptides prevent tissue damage by multiple mechanisms, including forming a gel-like matrix by cross-linking with mucins. Therapeutic effects of TFF have been shown in several animal models of gastrointestinal damage [19].

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published clinical practice guidelines for mucositis [20], [21]. These have resulted in a recommendation for the use of palifermin at a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplant to prevent oral mucositis in patients receiving high-dose CT and total body irradiation (TBI) followed by autologous stem cell transplantation for hematological malignancies. A suggestion has also been made against using GM-CSF mouthwash for the prevention of oral mucositis following CT in the transplant setting, since this agent was not found to be effective. No other guidelines for this class of agents have been possible to date due to insufficient or conflicting data.

As part of a comprehensive update of the MASCC/ISOO clinical practice guidelines for mucositis, the aim of this project was to systematically review the available literature and define evidence-based clinical practice guidelines for the use of cytokine and growth factor agents for the prevention and treatment of mucositis.

Methods

The methods are described in detail in papers by Bowen et al. [22] and Elad et al. [23] published elsewhere in this issue. Briefly, a literature search for relevant papers published before 31st December 2010 was conducted using OVID/MEDLINE, with papers selected for review based on defined inclusion and exclusion criteria.

Papers were reviewed by two independent reviewers, and data was extracted using a standard electronic form. Studies were scored for their Level of Evidence based on Somerfield criteria [24], and flaws were listed according to Hadorn criteria [25]. A well-designed study was defined as a study with no major flaws per Hadorn criteria.

Following panel consensus, findings from the reviewed studies were integrated into guidelines based on the overall Level of Evidence for each intervention. Guidelines were classified into three types: recommendation, suggestion, and no guideline possible. Guidelines were separated based on (1) the aim of the intervention (prevention or treatment of mucositis); (2) the treatment modality (RT, CT, chemoradiation, or high-dose conditioning therapy for HSCT); and (3) the route of administration of the intervention.

The list of intervention keywords used for the literature search of this section included: growth substances, cytokines, immunologic factors, colony-stimulating factors, amino acids, fibroblast growth factors, transforming growth factors, epidermal growth factor, platelet-derived growth factor, hepatocyte growth factor, vascular endothelial growth factor, somatomedins, interleukins, erythropoietin, granulocyte colony-stimulating factor, granulocyte–macrophage colony-stimulating factor, macrophage colony-

stimulating factor, thrombopoietin, ghrelin, keratinocyte growth factor, palifermin, milk-derived protein, whey protein, milk-derived growth factor extract, PV701, glucagon-like peptide 2, teduglutide, intestinal trefoil factor, carcinoembryonic antigen cell adhesion molecule 1, glutathione, FGF-7, FGF-20, CG 53135, velafermin, repifermin, and insuline-like growth factor.

In addition, the references of review papers were searched. We included papers reporting clinical studies with interventions including: palifermin, velafermin, repifermin, G-CSF, GM-CSF, EGF, TGF-beta, milk-derived growth factor extract, IL-11, ATL-10, and recombinant intestinal trefoil factor. We compared our findings with those of three systematic review papers including meta-analyses on mucositis interventions.

Results

Database searches found 1,718 papers. The full text of 156 papers was retrieved for detailed analysis, of which 31 were excluded immediately for not matching the inclusion criteria. Of the 125 remaining articles, the full text was assessed for methodological quality; 61 papers were removed based on failure to meet inclusion criteria, and 64 clinical studies were included in the review. Furthermore, three systematic reviews including meta-analyses on cytokines and growth factors were identified. Three studies were published after the cut-off date and are discussed as late breaking reports.

Agents belonging to the fibroblast growth factors superfamily

As summarized in Table 1, we continue recommending KGF-1 (palifermin) for the prevention of oral mucositis in patients with hematological malignancies receiving high-dose CT and TBI followed by autologous HSCT. Palifermin is administered intravenously in a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplantation. Our recommendation is based on the findings of a well-designed randomized clinical trial (RCT) [26, 27]. Evidence on the efficacy of palifermin in autologous HSCT without TBI conditioning is conflicting [28–34], and these rather small studies did not allow a guideline. In addition, no guideline could be provided for the use of palifermin in the setting of allogeneic HSCT with or without TBI [28, 35–37]. No guideline could be provided for the use of palifermin in the setting of CT for solid and hematological tumors [38–41] due to insufficient evidence, although a single center RCT of 49 patients, using a single dose of palifermin (180 μg/kg) before each cycle of CT prevented mucositis in multicycle CT for sarcoma [41]. In addition, no guideline could be provided for the use of palifermin in H&N RT due to insufficient evidence [42].

The meta-analysis performed by Worthington, and co-workers found a statistically significant benefit for palifermin to reduce the incidence of oral mucositis [43]. The meta-analysis included all available studies but did not discriminate between different clinical settings.

Studies performed on FGF-20 (velafermin) [8] and KGF-2 (repifermin) [9] did not allow a guideline due to insufficient evidence. The study on velafermin was a single center, phase I, open label, dose escalation study assessing the safety and tolerability of this growth factor. Similarly, the primary endpoint of the study on repifermin was to evaluate its safety. A preliminary analysis of data and patient-reported outcomes indicated that repifermin was well tolerated and seemed active in reducing oral mucositis. Nevertheless, both velafermin and repifermin did not become available on the market.

Granulocyte colony-stimulating factor

In our previous update, we were not able to provide a guideline for the use of subcutaneous G-CSF for the prevention of oral mucositis in patients treated with chemoradiation for H&N cancers. Two cohort studies did not find a benefit for the use of this growth factor [44, 45] in these patients, whereas a small study by Schneider et al. [46] reported only preliminary results. Since then, only one study on the use of systemic G-CSF for the prevention of oral mucositis induced by (C)RT for H&N cancers has been published [47]. This study reported a non-significant trend for a beneficial effect of this intervention but was closed prematurely because of low accrual. We did not change our previous conclusion that no guideline was possible because of insufficient evidence. The panel concluded that no guideline could be provided for or against the use of subcutaneous G-CSF for the prevention of mucositis in patients treated with CT since studies reported conflicting results [48, 49]. Crawford et al. [50] reported a beneficial effect, whereas a randomized controlled trial by Patte et al. [51] found that G-CSF was not effective to prevent mucositis in this setting (Table 1). In addition, no guideline could be provided for the use of a G-CSF mouthwash for the prevention of CT-induced oral mucositis [52].

The meta-analysis performed by Stokman et al. [53] concluded that systemic G(M)-CSF may prevent oral mucositis. Worthington et al. [43] concluded that there is weak evidence that systemic or topical G-CSF may be beneficial for the prevention of severe OM in H&N cancer patients undergoing RT.

Granulocyte–macrophage colony-stimulating factor

Our previous systematic review provided a suggestion against using GM-CSF mouthwash for the prevention of

Table 1 Summary of study findings for cytokines and growth factor agents

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	Author, year	Overall level of evidence	Guideline determination	Comments
hKGF-1 (palifermin)	Iv	Hematologic malignancies	HD-CT with TBI followed by auoHSCT	P	Spielberger (2004) [26], Stiff (2006) [27], Keefe (2006), [29]	II	Recommendation for the use of KGF1 (palifermin) in a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplantation for the prevention of oral mucositis	No evidence available for autologous HSCT patients not receiving TBI
hKGF-1 (palifermin)	iv	Hematologic malignancies	HD-CT without TBI followed by autoHSCT	P	Nasilowska-Adamska (2007) [28], Keefe (2006) [29], Tsirigotis (2008) [30], Horsley (2007) [31], Johansson (2008) [32], Verhagen (2008) [33], Kobbe (2010) [34]	III–IV	No guideline possible	
hKGF-1 (palifermin)	iv	Hematologic malignancies	HD-CT with and without TBI followed by alloHSCT	P	Nasilowska- Adamska (2007) [28], Blazar (2006)[35], Rzepecki (2007) [36], Langner (2008) [37]	II-III	No guideline possible	
hKGF-1 (Palifermin)	iv	Variety of solid and hematologic malignancies	CT	P	Meropol 2003 [38], Rosen (2006) [39], Schmidt (2008) [40], Vadhan-Raj (2010) [41]	II-III	No guideline possible	
hKGF-1 (Palifermin)	iv	H&N tumors	(C) RT	P	Brizel (2008) [42]	III	No guideline possible	Marginally effective in hyperfractionated RT
FGF-20 (Velafermin)	iv	Hematologic malignancies	HD-CT without TBI followed by autoHSCT	P	Schuster (2008) [8]	II	No guideline possible	Drug withdrawn
KGF-2 (Repifermin)	iv	Hematologic malignancies	HD-CT without TBI followed by autoHSCT	P	Freytes (2004) [9]	II	No guideline possible	Drug withdrawn
G-CSF	sc	H&N tumors	(C) RT	P	Abitbol (1997) [44], Mascarin (1999) [45], Schneider (1999) [46], Su (2006) [47]	III	No guideline possible	
G-CSF	sc	Solid cancers and pediatric non-Hodgkin lymphoma	CT	P	Katano (1995) [48], Viens (1996) [49], Crawford (1992) [50], Patte (2002) [51]	III	No guideline possible	
G-CSF	topical	Lymphoma	CT	P	Karthaus (1998) [52]	III	No guideline possible	
GM-CSF	mouthwash			P		II		

Table 1 (continued)

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	Author, year	Overall level of evidence	Guideline determination	Comments
		Hematologic and solid tumors	HD-CT with and without TBI followed by autoHSCT		Dazzi (2003) [54], van der Lelie (2001) [55]		suggestion not to use GM-CSF mouthwash for the prevention of OM in patients undergoing HSCT	
GM-CSF	Mouth-wash	Breast cancer	CT	P	Cartee (1995) [56]	III	No guideline possible	
GM-CSF	Mouth-wash	H&N tumors	(C) RT	P	Nicolatou (1998) [57], Nicolatou-Galitis, (2001) [58], Saarilahti (2002) [59] Mantovani (2003) [60], Sprinzl (2001) [61]	III	No guideline possible	Conflicting results not permitting a guideline
GM-CSF	syst	H&N tumors	CT	P	Chi (1995) [62]	III	No guideline possible	
GM-CSF	syst	H&N tumors	(C) RT	P	Kannan (1997) [63], Rosso (1997) [64], Wagner (1999) [65], McAleese (2006) [66], Ryu (2007) [67], Makkonen (2000) [68]	III	No guideline possible	
GM-CSF	syst	Hematologic and solid tumors	HD-CT with and without TBI followed by auto-or alloHSCT	P	Ifrah (1999) [69]. Nemunaitis (1995) [70], Gordon (1994) [71]	III	No guideline possible	
GM-CSF	Mouth-wash	H&N tumors	(C) RT	T	Mantovani (2003) [60], Rovirosa (1998) [72]	III	No guideline possible	
GM-CSF	Mouth-wash	Hematologic tumors	HD-CT with and without TBI followed by auto-or alloHSCT	T	Bez (1999) [73], Valcarcel (2002) [74]	III	No guideline possible	
GM-CSF	Mouth-wash	Solid tumors	CT	T	Ibrahim (1997) [75], Hejna (2001) [76]	III	No guideline possible	
GM-CSF	syst	H&N tumors	(C) RT	T	Rossi (2003) [77]	III	No guideline possible	
GM-CSF	syst	Colorectal cancers	CT	T	Masucci (2005) [78]	IV	No guideline possible	
TGF-β	Topical	Solid tumors and lymphoma	CT	P	Wymenga (1999) [81], Foncuberta (2001) [80]	II	No guideline possible	
TGF-β	Nutriti-on or mouthwash	Pediatric hematologic and bone tumors	CT	P	de Koning (2007) [82]	III	No guideline possible	
Milk-derived growth factor extract (PV701)	Topical	Lymphoma	HD-CT without TBI followed by autoHSCT	P	Prince (2005) [83]	III	No guideline possible	
EGF	Topical	Small cell lung cancer	CT	P and T	Girdler (1995) [84]	III	No guideline possible	Cave potential effect on tumor growth
EGF	Topical	H&N tumors	RT	P	Hong (2009) [85]	V	No guideline possible	Cave potential effect on tumor growth
EGF	Topical	H&N tumors	RT	T	Wu (2009) [86]	III	No guideline possible	Cave potential effect on tumor growth

Table 1 (continued)

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	Author, year	Overall level of evidence	Guideline determination	Comments
IL-11	sc	Hematologic malignancies	HD-CT with TBI followed by alloHSCT	P	Antin (2002) [87]	III	No guideline possible	Study was stopped because of severe side effects and mortality
ATL-104	Topical	Hematologic malignancies	HD-CT without TBI followed by autoHSCT	P	Hunter (2009) [88]	III	No guideline possible	
Recombinant human intestinal trefoil factor	Topical	Colorectal cancers	CT	P	Peterson (2009) [89]	III	No guideline possible	Promising results in patients treated with 5-FU containing regimens

alloHSCT allogeneic hematopoietic stem cell transplantation, *autoHSCT* autologous hematopoietic stem cell transplantation (C), *RT* (chemo)radiation therapy, *CT* chemotherapy, *EGF* epidermal growth factor, *HD* high-dose, *H&N* head and neck, *HSCT* hematopoietic stem cell transplantation, *iv* intravenous, *FGF* fibroblast growth factor, *5-FU* 5-fluorouicil, *G-CSF* granulocyte-colony stimulating growth factor, *GM-CSF* granulocyte–macrophage colony-stimulating growth factor, *IL-11* interleukin-11, *KGF* keratinocyte growth factor, *P* prevention, *RT* radiotherapy, *sc* subcutaneously, *syst* systemically, *T* treatment, *TBI* total body irradiation, *TGF-β* transforming growth factor-beta

oral mucositis in patients undergoing autologous or allogeneic HSCT [21]. This conclusion was mainly based on the results of a robust RCT by Dazzi et al. [54]. In the present update, an additional RCT by van der Lelie et al. [55] has been included, which provided additional evidence that GM-CSF mouthwashes are not effective to prevent oral mucositis in the HSCT setting. We continue to suggest not using preventative GM-CSF mouthwashes in these patients (Table 1). A well-designed dosing study for preventative GM-CSF mouthwashes by Cartee et al. [56] found no clear benefit for the use of this agent in patients treated with CT (including 5-fluorouracil, adriamycin, and methotrexate) for metastatic breast cancer. However, the panel decided that a guideline against the use of GM-CSF mouthrinses in all patients treated with various stomatotoxic CT regimens was not possible, since only one site-specific and highly mucotoxic CT regimen was evaluated in this study. Nicolatou-Galitis et al. [57, 58] reported results from a case series suggesting a preventative effect of GM-CSF mouthwashes on mucositis in patients receiving RT for H&N cancer, whereas controlled studies by Saarilahti et al. and Mantovani et al. [59, 60] reported only a marginal effect. In contrast, Sprinzl et al. [61] found no benefit (Table 1). Because of these conflicting results, no guideline could be provided for the use of GM-CSF mouthwashes for the prevention of (C)RT-induced oral mucositis. Prevention of mucositis using systemically administered GM-CSF has also been tested. One study found a benefit of this drug in H&N cancer patients treated with CT [62]. Whereas some studies found a benefit for preventative use of systemic GM-CSF in H&N cancer patients undergoing (C)RT [63–66], others did not confirm such effect [67, 68]. In addition, two studies indicated a benefit for systemically administered GM-CSF to prevent mucositis in the adult HSCT setting [69, 70], although in the latter study, oral mucositis was not a primary outcome. Gordon et al. [71] reported decreased duration of oral mucositis in pediatric HSCT with systemic GM-CSF. In sum, the panel concluded that the available evidence did not allow a guideline for the use of systemic GM-CSF to prevent oral mucositis associated with any of these cancer treatments.

Several studies addressed the use of GM-CSF mouthwashes for the treatment of established mucostitis in patients receiving (C)RT for H&N tumors [60, 72], HSCT[73, 74], and CT [75, 76]. Due to insufficient and conflicting evidence, no guideline was possible for the use of GM-CSF mouthwashes for the treatment of oral mucositis in any of these settings. In addition, there was not enough evidence to provide a guideline for the use of systemic GM-CSF for the treatment of oral mucositis in patients receiving H&N RT [77] or CT [78].

Clarkson et al. [79] and Worthington et al. [43] concluded that topical or systemic GM-CSF cannot be recommended for prevention or treatment of oral mucositis.

Transforming growth factor-beta, milk-derived growth factor extract, epidermal growth factor, interleukin-11, ATL-104 mitogen, and recombinant human intestinal trefoil factor

As shown in Table 1, no guidelines could be provided for any of these interventions due to insufficient evidence. TGF-β mouthwashes or enriched food were not effective to reduce oral mucositis in the used formulations [80–82]. A mouthwash with bovine milk-derived whey growth factors (PV-701) was well tolerated, and as compared to historical controls, the severity as well as the duration of oral mucositis seemed to be decreased in autologous HSCT recipients [83].

With respect to the use of topical EGF, the panel expressed concerns about the potential unfavorable effects of this growth factor on tumor growth [84–86], whereas the use of subcutaneous IL-11 was associated with severe side effects and mortality [87]. ATL-104 mouthwash reduced the duration of oral mucositis, whereas its effect on the incidence of mucositis was unclear [88]. Recombinant human intestinal trefoil factor oral spray was found to be safe and effective for the reduction of CT-induced oral mucositis in patients with colorectal cancers [89], but these limited data did not permit a guideline.

Discussion and late breaking reports

Although new evidence was included in the review process of the present update, this did not result in any changes of the clinical practice guidelines for cytokines and growth factor agents for the management of mucositis since the 2005 MASCC/ISOO review process [20, 21].

A suggestion was provided for *not* using GM-CSF mouthwash for the prevention of oral mucositis in patients undergoing autologous or allogeneic HSCT. With respect to the use of GM-CSF for the prevention or treatment of oral mucositis in other patient populations, we were not able to provide guidelines because of insufficient evidence (i.e., major flaws in study design and/or methods, according to the Hadorn criteria [25] and/or conflicting results).

We continue recommending the use of palifermin at a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplant to prevent oral mucositis in patients receiving high-dose chemotherapy and TBI followed by autologous stem cell transplantation for hematological malignancies, based on a well-designed RCT [26]. Although palifermin has been shown to be efficacious in this specific high-toxicity regimen, optimal dosing and timing of palifermin administration may be crucial and is likely to be different among different conditioning regimens.

In a high-dose melphalan conditioning regimen without TBI followed by autologous HSCT, the interval between the doses was shorter than in the registration study, and palifermin was associated with unfavorable side effects, including skin problems, orofacial swelling, mucosal ulceration, and taste alterations [33]. These observations warrant further investigation. The question whether palifermin reduces GVHD has been addressed in a number of clinical trials of allogeneic HSCT following myeloablative conditioning using cyclophosphamide plus TBI or CT only. None showed an impact on the occurrence of acute GVHD [28, 35, 37] or chronic GVHD [90]. The impact on mucositis was not consistent, with one study showing a decrease of oral mucositis only in patients conditioned with cyclophosphamide and TBI, but not in patients receiving a less mucotoxic regimen of busulfan and cyclophosphamide [35]. These findings are in line with a retrospective study on 251 patients published after the cut-off date for this review [91]. No mucositis measurements were available, but following palifermin administration similar to the registration study [26], mucositis-related adverse outcomes, including the mean number of days of total parenteral nutrition (13 versus 17 days, $P<0.001$), duration of patient-controlled analgesia (7 versus 12 days, $P=0.033$) and length of hospital stay (32 versus 38 days, $P=0.001$) were significantly decreased in TBI-based, but not in CT-based allogeneic HSCT. Palifermin did not affect GVHD.

No guideline could be provided for the use of palifermin in the setting of CT for solid and hematological tumors due to insufficient evidence [38–41], although the results of the single center study by Vadham-Raj et al. [41] are promising to prevent mucositis in multicycle CT for sarcoma.

In addition to the results of the study by Brizel et al. [42], in which post hoc analysis suggested that palifermin was marginally effective to reduce the duration of oral mucositis in hyperfractionated RT for H&N tumors, two publications of large multicenter, double-blind RCTs in patients treated with conventional 3D-chemoradiotherapy for H&N cancers became available after the cut-off date for the present update [92, 93]. Henke et al. [92] reported on patients that underwent postoperative CRT and received palifermin at doses of 120 μg/kg/week from 3 days before and continuing throughout the duration of treatment. A significant reduction of severe mucositis (WHO grades 3 and 4) was found in the treatment group (51 % versus 67 % in controls; $P=0.027$). Palifermin also delayed onset and significantly decreased the duration of severe mucositis (median 4.5 versus 22 days). However, patient-reported outcomes and treatment breaks did not differ between the treatment arms. Le et al. performed a parallel study of palifermin administered to patients undergoing definitive chemoradiotherapy for locally advanced H&N cancer using 180 μg/kg of palifermin or placebo prior to therapy and then weekly for 7 weeks [93].

In this study, the incidence of severe mucositis was also reduced in the treatment group (54 % versus 69 % in controls; $P=0.041$), the time to develop severe mucositis was longer, and the duration of severe mucositis was decreased in the palifermin arm. Disappointingly, other clinically relevant outcomes including mouth and throat soreness, opioid use, and treatment breaks did not differ significantly between the two arms. These studies suggest that palifermin may decrease the incidence of mucositis in H&N cancer patients treated with chemoradiotherapy based upon WHO scoring, while the impact upon patient symptoms is not clear. Palifermin did not affect survival observed 42 months post treatment, but follow-up studies are needed to confirm that the use of palifermin does not negatively affect tumor control and survival rates.

Recommendations for future research

Additional well-designed research is needed on cytokine and growth factor interventions. The clinical success of these biological agents depends on the choice of formulation, timing, route of administration, dosing, and stability of these agents. Furthermore, it is important to gain more insight into the pathobiology of mucositis as well as into pharmacogenetic variables and other genetic differences that underpin mucositis susceptibility.

TFF peptides protect mucosal cells from injury as well as contribute to epithelial reconstitution and should be considered as promising anti-mucositis agents [89]. A preclinical study suggested that a mouth rinse with genetically modified bacteria engineered to secrete human TFF-1 may provide future management tools [94].

Additional studies are necessary to assess the role of palifermin in patients treated for H&N cancers, particularly as therapeutic approaches continue to evolve. An intriguing development is the concept of hKGF gene transfer to salivary glands. In murine models, transgenic hKGF secreted from vector-transduced submandibular glands effectively protected oral mucosal epithelial cells from radiation injury [95]. This route of administration may prove to be beneficial in the future to prevent oral mucositis in patients being treated for H&N cancers.

Future studies should also include evaluating the safety and efficacy of using cytokines and growth factor agents for the management of mucositis in children and adolescents. In addition, future studies on these agents should not only focus on oral mucositis but should also be directed to protection from esophageal and gut mucosal barrier injury. However, cytokine and growth factor agents may have undesirable effects that may result from either stimulation of tumor growth or by interference with the tumor response to treatment. Therefore, the absence of tumor growth following the administration of stimulatory cytokines and growth factors must be confirmed in long-term follow-up studies.

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