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SPECIAL ARTICLE

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

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Abstract

Purpose To update the clinical practice guidelines for the use of growth factors and cytokines for the prevention and/or treatment of oral mucositis (OM).

Methods A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). The body of evidence for each intervention, in each cancer treatment setting, was assigned an evidence level. The findings were added to the database used to develop the 2014 MASCC/ISOO clinical practice guidelines. Based on the evidence level, the following guidelines were determined: recommendation, suggestion, and no guideline possible.

Results A total of 15 new papers were identified within the scope of this section and were merged with 51 papers that were reviewed in the previous guidelines update. Of these, 14, 5, 13, 2, and 1 were randomized controlled trials about KGF-1, G-CSF, GM-CSF, EGF, and erythropoietin, respectively. For the remaining agents there were no new RCTs. The previous recommendation for intravenous KGF-1 in patients undergoing autologous hematopoietic stem cell transplantation (HSCT) conditioned with high-dose chemotherapy and TBI-based regimens is confirmed. The previous suggestion against the use of topical GM-CSF for the prevention of OM in the setting of high-dose chemotherapy followed by autologous or allogeneic stem cell transplantation remains unchanged.

Conclusions Of the growth factors and cytokines studied for the management of OM, the evidence supports a recommendation in favor of KGF-1 and a suggestion against GM-CSF in certain clinical settings.

Keywords Oral mucositis · Growth factors · Cytokines · Systematic review · Guidelines

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Introduction

Oral mucositis (OM) remains a dose-limiting toxicity of cancer therapy, including chemotherapy (CT), radiotherapy (RT), radiochemotherapy (RT-CT), and HSCT. In addition to impairment of oral functions, severe OM can cause treatment interruptions and significant complications necessitating hospitalization, the use of narcotic analgesics, or additional nutritional support. These in turn may adversely affect overall cancer therapy outcomes and patients' quality of life. In addition, OM substantially increases the cost associated with cancer therapy [19].

Various agents have been investigated with respect to effectiveness in prevention or treatment of OM. As part of the continuous work of the Mucositis Study Group (MSG) of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO), clinical trials of therapeutic interventions are periodically reviewed to identify new agents and provide new evidence into the published clinical practice guidelines for the management of mucositis [45].

Growth factors (GF) are proteins that stimulate cell growth, proliferation, and differentiation, while cytokines are proteins or glycoproteins that modulate inflammatory and immune responses. Evidence supports an important role played by pro-inflammatory cytokines in the pathogenesis of OM [49]. The 2013 MASCC/ISOO clinical practice guidelines for mucositis management recommended the use of palifermin, a human recombinant keratinocyte growth factor (KGF-1) to prevent OM in patients receiving high dose CT or total body irradiation (TBI) followed by autologous HSCT for hematological malignancies and a suggestion was made against the use of granulocyte macrophage colony-stimulating factor (GM-CSF) mouthwash for the prevention of OM in the setting of high-dose chemotherapy followed by autologous or allogeneic HSCT [66]. No guideline was possible for any other GF or cytokine due to inconclusive evidence [66]. This paper describes the findings of the most recent systematic review conducted by MSG regarding GF and cytokines for the management of OM in cancer patients and the update of the MASCC/ISOO clinical practice guidelines on this topic.

Methods

The methods are described in detail in Ranna et al. [67]. Briefly, a search for relevant papers indexed in the literature from January 1, 2011 to June 30, 2016 was conducted using Pubmed/Web of Science/EMBASE, with papers selected for review based on defined inclusion and exclusion criteria.

Publications were reviewed by two independent reviewers, and data were extracted using a standard electronic form. Studies were scored for their level of evidence (LoE) based on Somerfield criteria [80], and flaws were listed according to Hadorn criteria [26]. A well-designed study was defined as a study with no major flaws per the Hadorn criteria.

Findings from reviewed studies were merged with the evidence from the previous MASCC/ISOO guideline update. Findings from the reviewed studies were integrated into guidelines based on the overall LoE for each intervention. Guidelines were classified into three types: recommendation, suggestion, and no guideline possible.

Guidelines were specified based on the following variables: (1) aim of the intervention (prevention or treatment of OM), (2) treatment modality (RT, CT, RT-CT, or high dose conditioning therapy for HSCT), and (3) route of administration of the intervention.

The list of intervention keywords used for the literature search of the growth factors and cytokines section is presented in the Methods paper [67].

Results

A total of 1091 papers were identified in the literature search: 684 from PubMed and 407 from Web of Science. After assessment of the abstracts, 1065 articles were excluded due to repetition across databases, non-clinical studies, meta-analyses, and reviews. One paper was transferred from another section of the guidelines update. Twenty-seven papers were retrieved for final review. After review of these full papers, five were transferred to other relevant sections in MSG according to the type of intervention (see list of sections in the Methods paper [67]). In addition, five papers were excluded as they did not satisfy the inclusion criteria (i.e. not related to mucositis). Ultimately, fifteen papers are included in this report and merged with fifty-one papers from the previous guidelines update. Additionally, thirteen papers that were reviewed in the previous guidelines update about interventions for which there is no new evidence are listed in this current guidene update.

KGF

Keratinocyte growth factors (KGF) are members of the fibroblast growth factor (FGF) superfamily [49]. Palifermin has pleiotropic activity [20]. It is believed to support the mucosal barrier integrity through its mitogenic activity on epithelial and endothelial cells, fibroblasts, and keratinocytes. KGF-1, also known as FGF-7, is involved in a number of cell survival activities [81]. This includes the suppression of apoptosis and activation of a redox-sensitive transcription factor, nerve growth factor-2 (Nrf2) that coordinates the expression of cytoprotective genes in keratinocytes, fibroblasts, and endothelial cells. Palifermin also upregulates interleukin-13 which

attenuates the effects of tumor necrosis factor (TNF) [81]. KGF may also downregulate other pro-inflammatory cytokines that are involved in the pathobiology of mucositis [49]. Two other members of the KGF family included in this review, FGF-20 (velafermin) and human recombinant KGF-2 (repifermin), have overlapping activity with KGF-1 as well as other actions that impact their effectiveness; these GF are described separately [21, 79].

As summarized in Table 1, five additional RCT and ten non-RCT studies were added to the previous review. For each given clinical situation, we concluded the following guidelines:

KGF intravenous (IV): Hematologic cancer — CT — prevention
Guideline: No guideline possible

The evidence available for the use of hKGF-1 intravenously in hematologic patients treated with CT is limited (LoE III). One RCT showed effectiveness in reducing severity of OM [7]. It was supported by another before-and-after study [77]. This study enrolled patients with OM in the first cycle of CT, and showed less severe and shorter OM following intravenous hKGF-1 in second cycle of CT [77]. Due to the limited evidence, no guideline is possible.

KGF (IV): Hematologic cancer — HSCT — prevention
Guideline: Recommendation (LoE I)

The use of KGF-1 intravenously is recommended for prevention of OM in patients with hematological cancer undergoing autologous HSCT with a conditioning regimen that includes high dose chemotherapy and TBI.

The current systematic review supports the previous guideline in this clinical setting. KGF-1 is recommended for the prevention of OM in patients with hematological malignancies receiving high dose CT and TBI followed by autologous HSCT. Our recommendation is based on five RCTs; four of them had no major flaws in the study design [4, 50, 51, 82, 84]. Two of these RCTs described the same patient population and are considered as a single study for the purpose of this analysis [82, 84]. Two new RCTs showing KGF-1 was effective in preventing OM were conducted in pediatric patients [50, 51]. Another RCT reported that KGF-1 was not effective in preventing OM in patients undergoing autologous HSCT without TBI conditioning [5]; therefore, the guideline is limited only to HSCT conditioned with TBI.

KGF (IV): Head and neck (H&N) cancers — RT-CT — prevention Guideline: No guideline possible

There were three RCTs in this category [8, 29, 48]. Although all available studies showed some effectiveness of KGF-1 for prevention of OM in H&N cancer patients undergoing RT-CT [8, 29, 48], analyses of reported results were inconclusive of the effectiveness. Two RCTs showed statistically significant reduction of severe OM incidence but the authors concluded that the clinical relevance of this finding is unclear considering lack of difference between the study and placebo group in regards to patient reported outcomes or treatment breaks [29, 48]. A previous study suggested that in a post hoc analysis KGF-1 was only marginally effective to reduce OM in hyperfractionated RT in H&N cancer patients [8].

KGF (IV): Solid cancers — CT — prevention
Guideline: No guideline possible

Two reports for the use of KGF-1 as preventive measure of OM in cancer patients receiving CT showed effectiveness (Table 1) [68, 90]. These studies were conducted in two different patient populations (colorectal cancer vs sarcoma) treated in different chemotherapy protocols (5-fluorouracil vs doxorubicin and ifosfamide). Another RCT in colorectal cancer patients treated with 5-fluorouracil compared 6 doses of KGF-1 to placebo and reached marginal significance ($p = 0.06$) [57]. No additional studies were found since the last guidelines update; therefore, there is no change to the guideline.

CSF

CSF are specific hematopoietic growth factors required for bone marrow progenitor cells to form mature blood cells. Data from basic science research suggest the mechanism of action of G-CSF in wound healing: Granulocyte colony-stimulating factor (G-CSF) stimulates development of neutrophils, eosinophils, and basophils, whereas granulocyte–macrophage colony-stimulating factor (GM-CSF) stimulates generation of cells belonging to the monocyte/macrophage lineage [37]. G-CSF and GM-CSF enhance the function of tissue neutrophils such as those present in the mucosa. Animal studies showed that GM-CSF promotes proliferation of keratinocytes and enhances wound healing including mucosal barrier injuries [3, 37].

For G-CSF, one additional RCT and two cohort studies were added to the previous review (Table 2). Based on the new evidence, a clinical category for G-CSF was added compared to the 2013 Guideline Update.

There was only one additional RCT regarding GM-CSF, and it was added to the previous guidelines (Table 3). The guideline for the use of GM-CSF (systemic or topical) remains the same as previous guideline.

G-CSF subcutaneous (SC): H&N cancers — CT — prevention
Guideline: No guideline possible

The RCTs regarding the effectiveness of G-CSF for the prevention of OM in H&N cancer patients are conflicting. A

Table 1 Studies reported for hKGF-1 (palifermin), overall level of evidence and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Guideline determination	Non-RCT studies
hKGF-1 Palifermin	Systemic (IV)	Hematol	CT	P	Bradstock 2014 [6]	Y (1)	III	NGP		Schmidt 2008 [77]—5 (Y)
	Systemic (IV)	Hematol	HSCT	P	Spielberger 2004 [82]	Y (1,2)	I	Recommendation	The use of KGF-1 intravenously is recommended for prevention of OM in patients with hematological cancer undergoing autologous HSCT with conditioning regimen that includes high dose CT and TBI.	Keefe 2006a [41]—8 (NA), Horsely 2007 [32]—4 (Y), Rzepecki 2007 [73]—4 (Y), Tsirigotis 2008 [87]—4 (N) Verhagen 2008 [93]—3 (N), Langner 2008 [46]—3 (Y), Johansson 2009 [36]—3 (N), Kobbe 2010 [44]—6 (Y), Abidi 2013—8 (NA), Goldberg, 2013 [24]—3 (Y), Nooka 2014—3 (Y), Lauritano 2014 [47]—6 (Y), Czyzewski 2014 [14]—6 (Y), Vitale 2014 [95]—6 (N), Nguyen 2015 [61]—4 (Y), Sakellari 2015 [76]—7 (Y), Morris 2016 [58]—4 (Y)
					Stiff 2006 [84]	Y (1,2)				
					Blazar 2006 [4]	Y (1)				
					Nasilowska-Adamska 2007 [59] (< 10% TBI)	Y(1,2)				
					Blijlevens 2013 [5]	N				
					Lucchese 2016a [50] (n = 27/27)[c]	Y (1)				
					Lucchese 2016b [51] (n = 24/22)[c]	Y (1)				
	Systemic (IV)	H&N	RT-CT	P	Brizel 2008 [8][a]	N	II	NGP		
					Henke 2011 [29]	Y(1,2)				
					Le 2011 [48]	Y(1)				
	Systemic (IV)	Solid ca.	CT	P	Meropol 2003 [57] b	N	II	NGP		
					Rosen 2006 [68]	Y (1)				
					Vadhan-Raj 2010 [90]	Y (1)				

Non-RCT studies key: 3—non-RCT, 4—cohort, 5—before and after, 6—case–control studies, 7—cross-sectional, 8—case series, 9—case report, 10—expert opinion

Effectiveness key: 1—mucositis severity, 2—mucositis duration, 3—pain severity, 4—pain duration

NGP no guideline possible, *HSCT* hematopoietic stem cell transplant, *H&N* head and neck, *RT* radiotherapy, *CT* chemotherapy, *hematol* hematological, *ca.* cancer, *PO* per os, *P* prevention, *Y* yes, effective, *N* no, ineffective, *NA* not applicable, conclusion about efficacy is not feasible, *IV* intravenous

[a] Post hoc analysis suggested that palifermin was marginally effective to reduce the duration of oral mucositis in hyperfractionated RT for H&N tumors [8]

[b] Primarily a dosing study; comparison of KGF-1 to placebo was not statistically significant, trend toward effectiveness [57]

[c] Pediatric patients

Table 2 Studies reported for granulocyte colony-stimulating factor (G-CSF), overall level of evidence and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Non-RCT studies
G-CSF (granulocyte colony-stimulating factor)	Systemic (SC)	Solid ca.	CT	P	Crawford 1992 [13]	Y (1)	III	NGP	Katano 1995 [40]—6 (Y), Viens 1996 [94]—3 (Y)
	Systemic (SC)	H&N	RT	P	Schneider 1999 [78]	N	III	NGP	Abitbol 1997 [1]—4 (N), Mascarin 1999 [54]—4 (N)
					Su 2006 [86]	N			
	Topical	Hematol	CT	P	Karthaus 1998 [39]	Y (1,2)	III	NGP	
	Systemic (SC)	Hematol	CT	P	Patte 2002 [64]	N	III	NGP	
	Topical (MW)	Solid ca.	CT	T				NGP	Wang 2016 [97]—4 (unclear)

Non-RCT studies key: 3—non-RCT, 4—cohort, 5—before and after, 6—case–control studies, 7—cross-sectional, 8—case series, 9—case report, 10—expert opinion

Effectiveness key: 1—mucositis severity, 2—mucositis duration, 3—pain severity, 4—pain duration

NGP no guideline possible, *HSCT* hematopoietic stem cell transplant, *H&N* head and neck, *RT* radiotherapy, *CT* chemotherapy, *hematol* hematological, *ca.* cancer, *PO* per os, *P* prevention, *Y* yes, effective, *N* no, ineffective, *unclear* results are unclear, *SC* subcutaneous, *MW* mouthwash

small RCT reported preliminary results suggesting G-CSF was not effective [78]. Another small RCT reported non-significant trend for a beneficial effect of G-CSF, and significant result for survival, but the study was closed prematurely due to low accrual [86]. The guideline remains no guideline possible.

G-CSF SC: Solid cancers — CT — prevention
Guideline: No guideline possible

A single new cohort study about G-CSF was published since the previous Guidelines Update [65]. This did not report data about OM rather about its tolerability. Overall, the evidence for this agent was insufficient to reach a guideline.

G-CSF (topical or systemic): Hematological cancers — CT — prevention
Guideline: No guideline possible

The panel concluded that no guideline could be provided for the use of G-CSF for prevention of OM in hematological cancer patients due to limited information about the effectiveness for either topical or systemic application [39, 64]. A RCT and a cohort study about this agent have been published since the last update investigating the use of G-CSF under the same clinical situation; these were excluded because they were not directly investigating OM [16, 85].

G-CSF (topical): Solid cancers — CT — treatment
Guideline: No guideline possible

One cohort study involved the use of topical G-CSF to treat OM in 14 patients [97]. Due to the limited evidence, no guideline was possible in this category.

GM-CSF (SC): H&N cancers — RT or RT-CT — prevention
Guideline: No guideline possible

The additional RCT reviewed in this update showed no effectiveness for systemic GM-CSF in prevention of OM for patients undergoing RT to the H&N. Therefore, the guideline remains the same. All studies in this clinical setting enrolled H&N patients treated with RT only [30, 55, 56]. The only exception was a single RCT which included a mix of H&N cancer patients treated with RT or RT-CT [72].

There was a comparator study in this clinical setting comparing GM-CSF to sucralfate [52]. The study concluded that there was no difference between the study groups in regard to OM grade, pain, and the use of analgesics.

Table 3 Studies reported for granulocyte–macrophage colony-stimulating factor (GM-CSF), overall level of evidence and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Guideline determination	Non-RCT studies
GM-CSF (granulocyte–macrophage colony-stimulating factor)	Systemic (SC)	H&N	RT or RT-CT	P	McAleese 2006 [56]	Y (1)	III	NGP		Kannan 1997 [38]—8 (Y), Rosso 1997 [70]—3 (Y), Wagner 1999 [96]—6 (Y)
					Ryu 2007 [72]	N				
					Hoffman 2014 [30]	N				
	Systemic (SC)	H&N	RT	T	Masucci 2005 [55]	Y (1)	III			
	Systemic (SC)	H&N	CT	P	Chi 1995 [12]	Y (1,2)	III	NGP		
	Systemic (SC)	H&N	CT	T			IV	NGP		Rossi 2003 [69]—4 (Y)
	Systemic (SC)	Hematol	HSCT	P	Nemunaitis 1995 [60]	Y (1)	III	NGP		Gordon 1994 [25][a]—3 (Y)
					Ifrah 1999 [35][b]	Y (1)				
	Topical (MW)	H&N	RT	P	Sprinzl 2001 [83]	N	III	NGP		Nicolatou 1998 [62]—8 (Y), Rovirosa 1998 [71]—4 (Y)
	Topical (MW)	H&N	CT or RT-CT	P						Mantovani 2003 [53]—3[c]
	Topical (MW/oral gel)	Solid ca./-hematol	HSCT	P	Van der Lelie 2001 [92]	N	II	Suggestion against	Suggestion against the use of topical GM-CSF for the prevention of OM in patients undergoing HSCT.	
					Dazzi 2003 [15]	N				
	Topical (MW)	Hematol	HSCT	T	Valcarcel 2002 [91]	N	III	NGP		Bez 1999 [2]—3 (Y)
	Topical (MW)	Breast ca.	CT	P	Cartee 1995 [11]	N	III	NGP		
	Topical (MW)	Solid ca.	CT	T	Hejna 2001 [28]	Y (2)	III	NGP		Ibrahim 1997 [34]—3 (Y)

Non-RCT studies key: 3—non-RCT, 4—cohort, 5—before and after, 6—case–control studies, 7—cross-sectional, 8—case series, 9—case report, 10—expert opinion

Effectiveness key: 1—mucositis severity, 2—mucositis duration, 3—pain severity, 4—pain duration

NGP no guideline possible, *HSCT* hematopoietic stem cell transplant, *H&N* head and neck, *RT* radiotherapy, *CT* chemotherapy, *hematol* hematological, *ca.* cancer, *PO* per os, *P* prevention, *MW* mouthwash, *SC* subcutaneous

[a] Pediatric

[b] The study assessed mucositis as a secondary endpoint and provides very limited information about it [60]. The study assessed mucositis as a secondary endpoint and provides very limited information about it [35]

[c] The study compared a "preventive" group to a "curative" group; no placebo control for any of these groups [53]

GM-CSF (SC): H&N cancers — RT — treatment
GM-CSF (SC): H&N cancers — CT — prevention
GM-CSF (SC): H&N cancers — CT — treatment
GM-CSF(SC):Hematological cancers — HSCT — prevention
GM-CSF(topical): H&N cancers — RT — prevention
GM-CSF(topical): H&N cancers — CT or RT-CT — prevention
GM-CSF(topical): Hematological cancers — HSCT — treatment
GM-CSF (topical): Breast cancer — CT — prevention
GM-CSF (topical): Solid cancer — CT — treatment
Guideline: No guideline possible

For these categories, there was limited evidence and no new data since the previous guidelines update (Table 3), therefore no guideline possible.

A RCT comparing GM-CSF mouthwash to sucralfate for the prevention of OM in H&N cancer patients treated with RT was reported [74]. The study concluded that GM-CSF mouthwash may be moderately more effective than sucralfate.

GM-CSF (topical): Solid/hematological cancer — HSCT — prevention
Guideline: Suggestion against topical use in HSCT (LoE II)

The evidence suggests that topical GM-CSF should not be used for the prevention of OM in patients undergoing HSCT.

Two RCTs [15, 92] showed no effectiveness of GM-CSF in the prevention of OM in this clinical setting. Accordingly, a guideline against the use of GM-CSF mouthwash for prevention of OM in patients undergoing autologous or allogeneic HSCT was made. Of note, the evidence for this guideline included a flawless large RCT study showing no effectiveness in regard to improving frequency of OM, mean duration of OM, OM-associated pain, and opioid use [15]. These studies were conducted when the conditioning regimen included TBI [92] and without TBI [15]. No new studies were found in this category; therefore, the guideline is unchanged.

EGF

Epidermal growth factor (EGF) is a polypeptide that plays an important role maintaining tissue homeostasis by regulating epithelial cell proliferation, growth, and migration [63]. EGF enhances mucosal wound healing and tissue generation, which was the basis for clinical studies in the treatment of OM.

There was one additional RCT using recombinant human epidermal growth factor (rhEGF) that was added to the previous guideline (Table 4).

rhEGF (topical): Hematological cancers — HSCT — prevention
Guideline: No guideline possible

A new RCT was identified in this clinical setting for this systematic review [43]. The RCT showed that rhEGF was effective in reducing duration of OM but not in reducing severity of OM. Considering the limited data, no guideline is possible.

rhEGF (topical): H&N cancers — RT-CT — prevention
Guideline: No guideline possible

A single RCT in this clinical category compared various doses of rhEGF to placebo for prevention of OM [98]. Approximately half of the patients received concurrent CT. The study concluded that rhEGF was effective. Considering the limited data in this category and the need of safety data on larger samples and longer follow up, no guideline is possible

rhEGF (topical): Solid cancer — CT — prevention
Guideline: No guideline possible

EPO

Erythropoietin (EPO) is a hematopoietic factor, produced mainly in the kidney via an oxygen-sensing mechanism. It stimulates the proliferation of erythroid progenitors in the bone marrow, leading to red blood cell production [10]. Recombinant human EPO is used to treat anemia. EPO also has anti-inflammatory effects by inhibiting NF-kB-dependent formation of a number of pro-inflammatory cytokines and carries antioxidant properties [9]. In one animal wound-healing model, the topical use of EPO-containing creams in wounds of diabetic rats showed a decrease in amount of apoptosis in a dose-dependent manner [27]. There are limited clinical studies of EPO efficacy in OM.

EPO (topical): Hematological cancers — HSCT — prevention
Guideline: No guideline possible

There was a single well-designed RCT reviewed in this systematic review about EPO for prevention of OM in patients undergoing autologous HSCT [33]. It demonstrated effectiveness of EPO mouthwash as a preventive measure reducing incidence and duration of OM (Table 4). This RCT is the first of its kind using EPO for OM. Due to the limited evidence, no guideline is possible.

Other interventions for which the evidence and guideline remains unchanged

Table 4 Studies reported for recombinant human epidermal growth factor (rhEGF) and erythropoietin, overall level of evidence and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Non-RCT studies
rhEGF (recombinant human epidermal growth factor)	Topical (oral spray)	Hematol	HSCT	P	Kim 2013 [43]	Y (2)	III	NGP	
	Topical[a]	H&N	RT-CT	P	Wu 2009 [98]	Y (1)	III	NGP	Hong 2009 [31]—(4) Y
	Topical (MW)	Small cell lung cancer	CT	P		N	III	NGP	Girdler 1995 [23]—(3) N
Erythropoietin	Topical (MW)	Hematol	HSCT	P	Hosseinjani 2015 [33]	Y (1,2)	II	NGP	

Non-RCT studies key: 3—non-RCT, 4—cohort, 5—before and after, 6—case–control studies, 7—cross-sectional, 8—case series, 9—case report, 10—expert opinion

Effectiveness key: 1—mucositis severity, 2—mucositis duration, 3—pain severity, 4—pain duration

NGP no guideline possible, *HSCT* hematopoietic stem cell transplant, *H&N* head and neck, *RT* radiotherapy, *CT* chemotherapy, *hematol* hematological, *ca.* cancer, *PO* per os, *P* prevention, *MW* mouthwash

[a] Oral spray then swallow

The current update did not yield any new studies for agents listed in Table 5. The guidelines remain the same as previously determined; no guideline is possible.

Discussion

This systematic review provides updated clinical guidelines for the use of cytokines and GF agents in the management of OM. New evidence was reported since the previous guidelines update [66] about KGF-1, G-CSF, GM-CSF, EGF, and EPO.

In support of previously determined guidelines, the current evidentiary update continues recommending the use of KGF-1 (IV) for the prevention of OM in patients with hematological cancer undergoing autologous HSCT when the conditioning regimen includes TBI. The LoE for this recommendation was upgraded from LoE II to LoE I.

Interestingly, this guideline is based on evidence in adult patients; however, there is new promising evidence indicating that this guideline may also be applicable for pediatric patients [50, 51]. This guideline is limited to HSCT where its conditioning includes TBI because the evidence about efficacy was available exclusively when TBI was delivered [4, 50, 51, 82]. This was reported also in a large retrospective comparative study demonstrating that palifermin decreased total parenteral nutrition, patient controlled analgesia, and length of stay at the hospital following TBI-based but not chemotherapy only–based -HSCT [24] allogeneic.

Table 5 Interventions for which the evidence and guideline are unchanged, based on existing literature (adapted from Raber-Durlacher [66])

Aim	Agent	Route of administration	Patient population	Treatment modality	Guideline
P	Velafermin (FGF-20)	Systemic (IV)	Hematol	Auto HSCT	NGP
P	Repifermin (KGF-2)	Systemic (IV)	Hematol	Auto HSCT	NGP
P	Milk-derived protein extract	Topical (MW)	Hematol	Auto HSCT	NGP
T	Recombinant human intestinal trefoil factor (rhITF)	Topical (oral spray)	Colorectal ca.	CT	NGP
P	Recombinant human interleukin-11 (IL-11)	Systemic (SC)	Hematol	Allo HSCT	NGP
P	ATL-104	Topical (MW)	Hematol	Auto HSCT	NGP
P	Transforming growth factor-B (TGF-B)	Topical (MW)	Solid cancer/hematol	CT	NGP
P	Transforming growth factor-B (TGF-B)	Topical (MW or TGF-β2-enriched feeding)	Hematol/bone tumor[a]	CT	NGP

[a] Pediatric patients

NGP no guideline possible, *HSCT* hematopoietic stem cell transplant, *H&N* head and neck, *RT* radiotherapy, *CT* chemotherapy, *hematol* hematological, *ca.* cancer, *PO* per os, *P* prevention, *IV* intravenous, *MW* mouthwash, *SC* subcutaneous Auto autologous, Allo allogeneic

While the 2013 guideline was limited to autologous HSCT, there is increasing evidence that this may be applicable for allogeneic HSCT [4, 51, 59]. However, the evidence in allogeneic HSCT was in variable patient populations in regard to the patient's age and inclusion of TBI in the conditioning regimen. Therefore, the scope of the current guideline remained for autologous HSCT only.

It should be highlighted however that there is regional variation in the ability to use KGF-1 (Palifermin, Kepivance). Since the previous MASCC/ISOO guideline update was published, the approval for the use of this drug was withdrawn within the European Union by the European Medicines Agency (EMA) [17]. Per the information on the EMA website, the withdrawal was at the request of the marketing authorization holder, which notified the European Commission of its decision to permanently discontinue the marketing of the product for commercial reasons [18]. Conversely, the drug is still approved for use in the USA by the FDA [88]. This was reconfirmed on the US National Cancer Institute (NCI) webpage on March 2018 [89].

In the 2013 guideline update, a suggestion against the use of topical GM-CSF for the prevention of OM in patients undergoing HSCT was made. No new evidence has been reported for this agent in the clinical setting since 2013. Therefore, this guideline remains valid.

New evidence was published that introduced certain agents in a new clinical setting. These included G-CSF in patients with solid cancers treated with CT and rhEGF and EPO in patients undergoing HSCT. However, the evidence in these new categories did not reach the threshold for a guideline.

It was reported that when the intervals between doses of palifermin were shorter, as happened in the high-dose melphalan conditioning regimen, without TBI, prior to autologous HSCT, there were more adverse effects including skin problems, orofacial swelling, mucosal ulceration, and taste alterations [93]. Importantly, palifermin did not affect graft-versus-host disease (GVHD), graft failure, or relapse [24]. These findings were supported by a study from the Center for International Blood and Marrow Transplant Research (CIBMTR) database which reported that in univariate analyses, two-year survival and disease-free survival rates after allogeneic HSCT and after autologous HSCT were similar between palifermin-treated patients and matched controls [75]. Additionally, in multivariate analysis, palifermin did not significantly increase the risk of mortality or relapse compared with matched controls. No significant differences in rates of

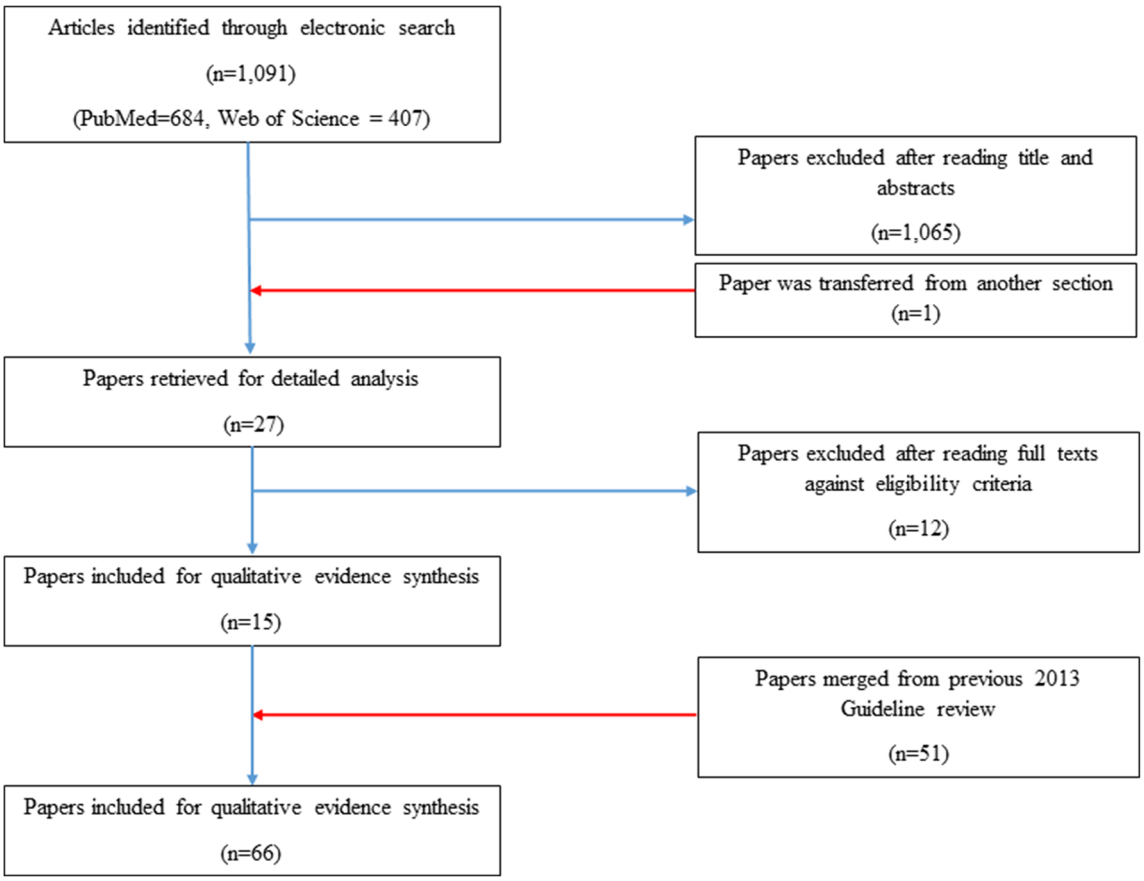

Fig. 1 Article flow chart throughtout the systematic review

acute or chronic GVHD were observed between palifermin-treated patients and matched controls [75]. Nevertheless, these long-term safety data were obtained at 31 months following administration of palifermin. To our best knowledge, there are no data regarding the 5-year relapse and overall survival post-administration of palifermin for prevention of OM.

A Cochrane review about GF and cytokines for the prevention of OM concluded that in regard to adult patients undergoing HSCT, the group was less confident about a benefit for KGF-1 because of multiple factors involved in that population, such as whether or not they received TBI, and whether the transplant was autologous or allogeneic. Likewise, the Cochrane group concluded that KGF-1 was beneficial in the prevention of OM in adults who are receiving: (a) RT to the H&N with cisplatin or fluorouracil or (b) CT alone for mixed solid and hematological cancers. Noticeably, there was difference between the MASCC/ISOO methodology and the Cochrane group methodology in regards to inclusion of RCTs that calculated the efficacy based on area under the curve, in the clinical interpretation of the evidence in H&N cancer patients [8, 29, 48], and in the separation of evidence based on the cancer type [6, 57, 68, 90].

KGF-1 (palifermin) is administered systemically in all the RCTs that reported its use. Therefore, the question of safety is of greater importance relative to topical agents. Of relevance to the studies about prevention of OM with KGF-1 in patients with H&N cancer, KGF can induce proliferation of epithelial cell lines. Until long-term safety data about KGF in patients with H&N cancer are available, the interpretation of the data about the clinical efficacy needs to be considered carefully.

The fact that various growth factors (KGF, G-CSF, GM-CSF, EGF, and EPO), each effecting a different cell line (keratinocytes, granulocytes, macrophages, fibroblasts, erythrocytes, respectively), were suggested as interventions for OM reflects the complexity of the healing process of OM and the delicate balance needed between all these components to maintain the oral mucosal integrity.

Since the cutoff date for the literature review, a RCT was published testing the efficacy of topical rhEGF as an oral spray for the prevention OM in patients undergoing HSCT [42]. This report was an extension of a previous publication [43] concluding that rhEGF was effective for the prevention of OM. However, the later and larger report concluded that rhEGF was ineffective for the prevention of OM. Another RCT, designed as a comparator study, used rhEGF as a control while testing a Chinese medicine for the prevention of RT-associated OM [97]. A RCT comparing IV KGF versus chlorhexidine in pediatric patients with hematological cancers treated with CT reported that KGF reduced the severity of OM [22].

In summary, for the interventions reviewed in this paper, the available evidence supported a recommendation for KGF-1 (palifermin) for the prevention of OM in a well-defined clinical setting. Likewise, based on the previously reported evidence, the suggestion against topical GM-CSF for the prevention of mucositis is validated. Considering the growing body of evidence, the guidelines about the agents covered in this section will require updating in the future (Fig. 1).

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Compliance with ethical standards

Conflict of interest Per MASCC Guidelines Policy, employees of commercial entities were not eligible to serve on this MASCC Guidelines Panel. PB has served an advisory role for AstraZeneca, Helsinn, and Kyowa Kyrin and received grants from Merck, Kyowa Kyrin, and Roche. RVL has served as a consultant for Alira Health, Colgate Oral Pharmaceuticals, Galera Therapeutics, Ingalfarma SA, Monopar Therapeutics, Mundipharma, and Sucampo Pharma; has received research support to his institution from Galera Therapeutics, Novartis, Oragenics, and Sucampo Pharma; and has received stock in Logic Biosciences. SE Discloses no conflict of interest in regards to the subject matter, and serve as a consultant for Falk Pharma outside the submitted work.

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