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口腔清掃方法の違いが経口挿管患者の口腔衛生状態に与える影響の検討

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【目的】本研究では，口腔清掃方法の違いが口腔衛生状態に与える影響を明らかにすることを目的とし，経口挿管患者の口腔衛生状態の実態を調査するとともに，口腔衛生状態の問題の改善が口腔清掃方法によって異なるかどうかを検討した．

【対象と方法】本学病院集中治療部に入院した患者のうち，経口挿管患者162名を対象とした．口腔清掃でQケア®（Sage社製）を使用した群（介入群，87名），および市販の歯ブラシおよびスポンジブラシを用いた群（対照群，75名）に分け，口唇，歯，口腔粘膜，歯肉，舌，口腔乾燥，歯の状態，口臭の問題を3段階で評価した．また初回評価時には舌の *Candida* 菌量を測定した．

【結果】初回評価時の口腔内の問題点では約60%に舌の問題が，約40%に口唇の異常がみられた．*Candida* 属真菌は約60%の対象者から検出された．その後の，粘膜および口腔乾燥の問題は介入群で有意に高い割合で改善された．改善までの期間は多くの項目で介入群のほうが短かった．また，*Candida* 属真菌の数と口腔衛生状態の問題点の変化の関連では，舌の項目では介入群，対照群いずれも改善が得られた対象者では *Candida* 属真菌の検出量が少なかった．

【結論】介入群では抗菌作用，湿潤作用などを有した薬液が用いられ，それによって舌苔や粘膜の乾燥などが改善されたものと考えられた．また，口腔内の日和見菌である *Candida* 属真菌が検出された対象者では，舌に生じる問題点の改善が得られにくい可能性が示唆された．

Screening	
Y ☐ N ☐	1. Patient takes 9 or more medications
Y ☐ N ☐	2. Patient receives one or more of the following classes of high-risk medications • Anticoagulant • Benzodiazepine • Insulin • Narcotic • Psychotropic
Y ☐ N ☐	3. Patient has cognitive impairment, end-stage renal disease, diabetes, heart failure, pacemaker
Y ☐ N ☐	4. Patient has questions about his/her medications (purpose, schedule, etc.)

Figure 1. Level 1 pharmacy screening tool.

have greater utility in primary care practices with fewer frail elderly adults to identify and target high-risk individuals for pharmacy intervention. Clinics adopting the screen may choose to train nursing personnel or add lists of commonly used psychotropic medications or benzodiazepines to aid staff recognition of these agents. Furthermore, new data and consensus on medication safety may influence future iterations of the pharmacy screen.[8]

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IMMEDIATE EFFECT OF DENTURE WEARING ON SWALLOWING IN REHABILITATION HOSPITAL INPATIENTS

To the Editor: Some people do not wear dentures even after completion of acute treatment for life support and the start of oral feeding, and others have to start oral feeding without dentures because their dentures do not fit well.[1,2] Eating without dentures may exacerbate ingestion, mastication, and swallowing disorders, but it is not known whether feeding and swallowing functions differ in individuals with and without dentures. This study involved eight elderly adults (6 male, 2 female, mean age 82.4) transferred to a recovery rehabilitation unit after completion of acute treatment who did not wear dentures when eating. Their primary diagnoses were disuse syndrome after cerebral infarction (n = 2), after bone fracture surgery (n = 2),

Table 1. Qualitative and Quantitative Evaluations of Participants with and without Dentures

		Without Dentures				With Dentures			
Sex	Age	Aspiration	Pharyngeal Residue	Laryngeal Elevation Start Time	Pharyngeal Transit Time	Aspiration	Pharyngeal Residue	Laryngeal Elevation Start Time	Pharyngeal Transit Time
Male	83	–	–	−0.27	0.33	–	+	−0.30	0.27
Male	96	–	+	−0.20	0.50	–	+	−0.17	0.37
Male	70	–	–	−0.40	0.37	–	–	−0.37	0.37
Male	91	–	–	−0.43	0.50	–	–	−0.20	0.33
Female	87	–	–	−0.23	0.47	–	–	−0.13	0.47
Male	80	–	++	−0.30	0.50	–	++	−0.27	0.40
Female	77	–	++	1.17	2.03	–	++	1.00	1.70
Male	75	–	–	−0.30	0.20	–	–	−0.33	0.20

– = no aspiration or pharyngeal residue; + = slight aspiration and pharyngeal residue; ++ = obvious aspiration and pharyngeal residue.

and after pneumonia (n = 4). None had any occlusal contact without dentures. Videofluorography (VF) was performed because they had feeding and swallowing disorders on admission, but none of the subjects wore dentures at that time. So to perform further VF assessment, their old dentures were repaired or relined on the day of the study so that feeding and swallowing functions with and without dentures could be compared. VF assessment was performed during ingestion and swallowing of 1 spoon of yogurt (4 mL), and a dentist and an otolaryngologist with 10 years of experience in dysphagia rehabilitation analyzed the findings. Aspiration and pharyngeal residue were assessed as none (−), slight (+), and obvious (++) for qualitative evaluation. Time to initiation of laryngeal elevation (the difference between the time when the tip of the food bolus reached the hypopharynx and the time to initiation of laryngeal elevation, in which a smaller difference indicated earlier initiation of laryngeal elevation) and pharyngeal transit time (the difference between the time when the tip of the food bolus passed the inferior border of the mandible and when the end of the food bolus passed the esophageal orifice) were determined for quantitative evaluation, according to previous studies.[3] These temporal parameters of individuals with dentures were compared with those of individuals without dentures to evaluate the immediate effect of wearing dentures. None of the subjects aspirated the yogurt. In addition, the amount of pharyngeal residue with dentures, determined subjectively, did not differ significantly from that without dentures. Time to initiation of laryngeal elevation with dentures (−0.10 ± 0.45 seconds) did not differ from that without dentures (−0.12 ± 0.53 seconds) ($P = .56$), but mean pharyngeal transit time was 0.51 ± 0.49 seconds with and 0.61 ± 0.58 seconds without ($P = .04$) (Table 1). Wearing dentures decreased pharyngeal transit time. Extension of pharyngeal transit time increased risk of aspiration,[4,5] so wearing dentures may decrease the risk of aspiration. Pharyngeal transit time varies depending on individual tongue force, which moves food into the pharynx, and enlargement of the esophageal orifice by laryngeal elevation. A previous study[6] found that swallowing time was shorter in edentulous subjects with new, well-fitting prostheses than in those with old prostheses and suggested that the reason was that the tongue did not need to support an ill-fitting prosthesis or that better occlusal stability facilitated movement of the suprahyoid muscles. A study of the range of hyoid bone and larynx movements and deglutition time in subjects with a mean age of approximately 50 found that hyoid bone and larynx movements were significantly greater in edentulous subjects than in denture-wearing and dentate subjects when swallowing saliva and that deglutition time was shortest in edentulous subjects without dentures,[7] although the subjects in the current study were disuse syndrome patients with muscle weakness who could not elevate the larynx and hyoid bone sufficiently when swallowing without wearing dentures. Therefore, it was considered that their deglutition time decreased when wearing dentures. Efforts have continued to recruit subjects who were not wearing dentures but could use repaired or relined dentures on the study day to provide a scientific basis for the results of this study.

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integrity of the data and the accuracy of the data analysis. Study concept and design: Masuda, Yoshida. Acquisition of data: Yoshida, Masuda, Amano. Analysis and interpretation of data: Yoshida, Masuda. Drafting of the manuscript: Yoshida. Critical revision of the manuscript for important intellectual content: Akagawa. Study supervision: Akagawa.

Sponsor's Role: None.

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CASE REPORTS

VITAMIN C DEFICIENCY IN AN ELDERLY ADULT

To the Editor: A 92-year-old woman, Mrs. GS, presented with widespread bruising and swelling in her lower limbs. She had moderate dementia, high blood pressure, hypothyroidism, depression, congestive cardiac failure, pemphigoid, and constipation. She was taking bumetanide 1 mg three times per day, lactulose 10 mL/d, paroxetine 20 mg/d, perindopril 2 mg every night, prednisolone 10 mg/d, Senokot 2 tablets every night, and thyroxine 150 μg/d. On examination, she was found to have pitting edema in both lower limbs and large ecchymosis in both legs. Routine blood tests showed normal complete blood count, normal coagulation studies, normal albumin, a thyroid stimulating hormone (TSH) level of 7.57 mIU/L (normal range 0.4–4.0 mIU/L), blood urea nitrogen (BUN) of 30.5 mg/dL (normal range 7–21 mg/dL), creatinine of 1.05 mg/dL (normal range 0.6–1.2 mg/dL), and slightly high liver function tests with a gamma-glutamyltransferase (GGT) of 246 IU/L (normal range 0–42 IU/L). It was suspected that these symptoms and signs may have been due to steroid treatment, which was reduced. Management also involved increasing thyroxine to 175 μg/d. Despite these changes to her medication, there was no significant improvement. It was thus decided to take a vitamin C level, which was found to be 0.12 mg/dL (normal range 0.5–1.5 mg/dL). Vitamin C was started at a dose of 1 g/d, and marked reductions in bruising and lower limb edema were seen within 1 week. Vitamin C was then continued at 100 mg/d, and all previous abnormal signs disappeared within 3 weeks.

Scurvy is a disease caused by prolonged severe dietary deficiency of ascorbic acid, leading to capillary hemorrhages and defective growth of fibroblasts, osteoblasts, and odontoblasts, resulting in impaired synthesis of collagen, osteoid, and dentine. It is characterized by hemorrhagic gingivitis affecting especially the interdental papillae, subperiosteal hemorrhages, bone lesions seen on radiography, perifollicular hemorrhages, and frequently petechial hemorrhages (especially in the lower limbs).[1]

Other manifestations include edema, exertional dyspnea, and emotional disturbances that can include apathy, depression, bipolar disorder, and anxiety. Sudden death may occur as a result of cerebral or myocardial hemorrhage. Megaloblastic anemia, usually due to concomitant iron or folate deficiency or both, is usual.

Scurvy is rare in industrialized countries because of technological developments including food processing and transportation, although recent case reports of scurvy indicate that vitamin C deficiency may be more prevalent than generally assumed.[2] Low vitamin C levels are common in adults living on low incomes and in certain populations with poor nutrition, including elderly persons living alone, those living in poverty, institutionalized and chronically ill individuals, alcoholics, and individuals with psychiatric disorders.[3]

The main criteria for diagnosing scurvy include a history of dietary inadequacy of vitamin C, clinical manifestations characteristic of a scorbutic state, biochemical indices of low levels of vitamin C in the blood or urine, and a clinical response to vitamin C supplementation with resolution of the manifestations of the disease within a few days.[4]

The differential diagnosis includes clotting factor deficiencies, leukemia, gingivitis, platelet dysfunction, senile purpura, and vasculitides (e.g., Wegener's granulomatosis).

Biochemical evaluation of vitamin C status in humans is usually conducted through a determination of serum (plasma) ascorbic acid levels. Serum levels of ascorbic acid show a linear relationship with vitamin C intake. Reference ranges for plasma vitamin C levels are 0.6 to 2.0 mg/dL, with levels below 0.3 mg/dL suggesting significant deficiency.[5,6]

Treatment of scurvy is simple and effective. In adults, the usual dose is 1 to 2 g of vitamin C administered daily for 2 to 3 days, followed by 500 mg per day for 2 weeks. Afterward, 100 mg of vitamin C should be given daily for 1 to 3 months.[3] Orally administered vitamin C is well absorbed from the gastrointestinal tract. It can also be given intravenously or intramuscularly in special circumstances. A diet rich in vitamin C should be initiated simultaneously. People respond quickly to oral therapy, and the prognosis is excellent. Spontaneous bleeding ceases within 1 day; bleeding, sore gums heal in 2 to 3 days; and ecchymoses usually heal within 12 days.

Early recognition of scurvy can be difficult because symptoms are often vague and nonspecific and can mimic a variety of more-common conditions. Physicians should consider vitamin C deficiency when presented with a purpuric rash and edema in vulnerable elderly adults and treat promptly, because this condition is readily amenable to treatment.

頭頸部がん患者に対して口腔ケアを行った2症例

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Case Report of Oral Care for the Head and Neck Cancer Patients

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症例報告レビュー

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キーワード：口腔ケア，頭頸部がん，周術期管理，合併症

緒　　言

頭頸部がんとは，頭部，顔面，頸部に生じる悪性腫瘍の総称である。鎖骨・胸骨より頭側で頭蓋底までの範囲のうち，脳や脊髄といった中枢神経系や眼窩内から発生する悪性腫瘍は除外される。日本におけるがん罹患者数は2007年で約71万人と推計されているが，頭頸部がんはそのうち約3万人である[1)]。

頭頸部がん治療においては，外科手術，化学療法，放射線治療を単独あるいは組み合わせて行われるが，同時に合併症は避けて通ることのできない課題である。そのうち，口腔内に出現する合併症にはさまざまなものがある。例えば，再建手術では，瘻孔形成に伴う膿瘍形成，創部感染，皮弁壊死，誤嚥性肺炎がある。また，化学療法では，口腔粘膜炎や口腔カンジダ症がある。さらに，放射線治療では，口腔粘膜炎や口腔カンジダ症に加え，唾液腺障害による口腔乾燥がある。

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これらの合併症を予防，軽減するために口腔ケアが重要であるといわれている。

岡山大学病院では2012年4月より，医師・歯科医師・歯科衛生士・歯科技工士・看護師・薬剤師・言語聴覚士などの多職種がチーム医療を展開する頭頸部がんセンターが設立された。同院予防歯科では，センター開設前より周術期および退院後の継続的な口腔ケアを担当している。その中から2症例について報告する。

症　　例

症例1

患　者：65歳，男性

初診日：2013年4月

主　訴：舌の裏の「できもの」が気になる。ブラッシング時に口腔粘膜がしみる。

現病歴：2012年6月頃から口の中の違和感を自覚していたが，改善が見られないため，同年8月に某市民病院耳鼻咽喉科を受診したところ，口腔底がん（T2N2cM0）との診断を受け，岡山大学病院耳鼻咽喉科へ紹介された。術前化学療法（シスプラチンと5-フルオロウラシルの併用），外科手術（口腔底腫瘍切除，下顎骨辺縁切除，両側頸部郭清術）が行われ，さらに，術後放射線治療（50.4Gy）を受けた。その後も定期的に外来受診にて経過観察を行っていたが，2013年4月に舌下面に3.5cm程度の硬結を伴う腫瘤を認めたため，生検を行ったところ，口腔底がん（T4aN0M0）再発との診断を受けた。術前化学療法（5-フルオロウラシル，シスプラチン，ドセタキセルの併用）と外科手術（下顎骨区域切除，舌可動部切除，肋骨前鋸筋再建）の適応となった。ブラッシング時に口唇に痛みを感じ，口腔内清掃に困難をきたしていたため，当院予防歯科へ紹介となった。

全身既往歴：特記すべき全身疾患はない。喫煙歴は1日20本×40年間であったが，現在は禁煙している。

1．初診時現症

1）口腔内所見

現在歯数は上顎13本，下顎5本の合計18本であった。全顎的にコンポジットレジンまたは全部鋳造冠による修復がなされていた。また，11および21に辺縁不適合なレジン前装鋳造冠が装着されていた。動揺歯は認められなかった。O'Learyの Plaque Control Record（PCR）[2]は58.3%であり，下顎両側大臼歯へのプラークの付着を多く認めた。歯周ポケット深さ（probing depth：PD）の測定については，歯周ポケットプローブ（CP-11カラーコードプローブ®，Hu-Friedy，USA）を用いて，1歯6点法により行った。その結果，平均PDは3.1 mmであり，プロービング時出血（BOP）割合は24.1%であった（表1および図1）。

2）デンタルエックス線検査所見

全顎的に歯根の1/3～1/4程度に及ぶ水平性および垂直性の歯槽骨吸収が認められた。また，36の根分岐部には透過像が認められた（図2）。

3）口腔粘膜所見

前述のごとく，2012年に口腔底がんおよび下顎骨辺縁切除を受けており，下顎正中部には皮弁による再建がなされていた。舌下面正中に3.5cm×2.5cmの腫瘤を認めた。また，下口唇に多数のアフタを認めた。

4）白血球数

初診時における白血球数は5290/μlであった。

2．治療方針

口腔底がんおよび下顎骨辺縁切除を受けており，皮弁再建がなされている。そのため，下顎両側臼歯部のプラークコントロールが不良となっており，感染源の除去と併せてセルフケア方法の提案および指導が必要であると考えた。また，化学療法による口腔粘膜炎発症の可能性があるため，口腔粘膜のこまめな観察と消炎処置が必要であると考えた。

3．治療経過

1）術前化学療法中の経過

術前化学療法開始前に，全顎的なスケーリングおよび歯面研磨を行った。なお，下顎はがんの部位を含んでいるため，歯肉縁上のスケーリングにとどめた。ブラッシング時の口腔粘膜の疼痛に対しては，軟毛タイプの歯ブラシ（エラック541ソフト®，ライオン歯科材株式会社，東京）の使用を勧めた。また，歯磨剤に含まれる発泡剤であるラウリル硫酸ナトリウムが口腔粘膜への刺激の原因となるため，無配合の歯磨剤（バイオティーントゥースペースト®，ティーアンドケー株式会社，東京）の使用を勧めた。その結果，ブラッシング時の口腔粘膜の疼痛は消失し，早期に口腔清掃状態が改善した（PCR：58.3%→23.6%）。また，平均PDは2.0 mmに，BOP割合は2.8%に減少した（表2）。

下口唇のアフタに対しては，抗炎症作用を有する軟膏（アズノール®軟膏0.033%，日本新薬株式会社，京都）の塗布を行うことで消退した。化学療法に伴い白血球数は減少し，終了後5日目には1260/μlまで低下した。その後は7000/μlまで回復した。化学療法中お

表1　初診時の歯周組織検査結果（症例1）

上顎	頬側	2 1 6		2 2 2	3 2 2	2 1 1	1 1 2	2 1 1	4 2 2	3 2 3	3 3 2	2 3 3	4 2 3	3 2 6	3 3 3								
	口蓋側	5 4 8		5 4 4	4 3 4	3 3 3	3 3 3	2 2 3	6 3 4	4 4 5	5 5 3	3 3 4	4 4 4	5 4 4	3 5 3								
	動揺度	0		0	0	0	0	0	1	1	0	0	0	1	1								
歯式		8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8						
下顎	動揺度		0	0	0										0		0						
	舌側		3 3 3	4 5 4	5 3 2										3 3 3		3 3 3						
	頬側		2 2 2	2 2 2	3 2 2										4 3 2		3 3 6						

赤字はBOP(+)の部位を示す。

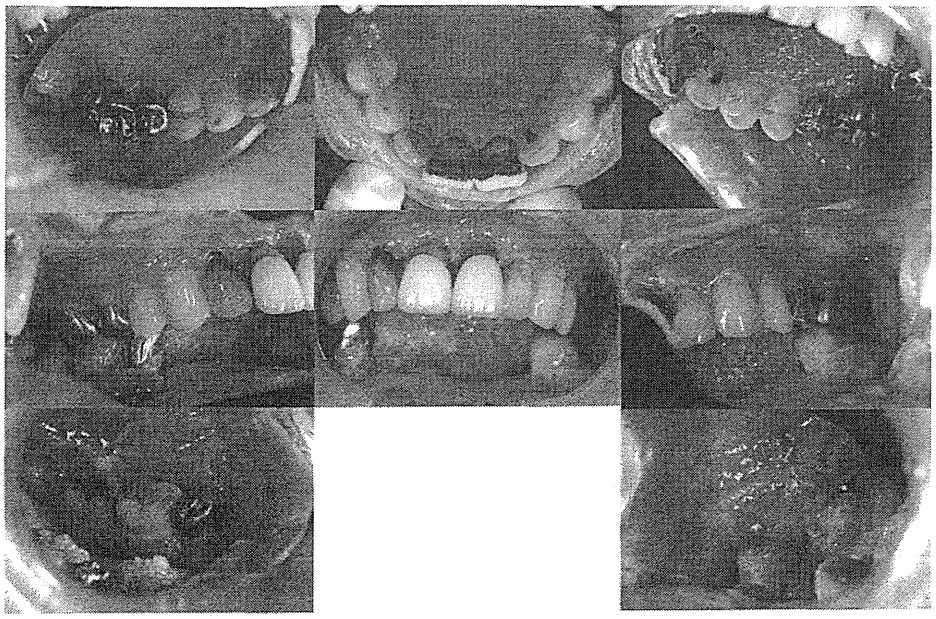

図1　初診時の口腔内状態（症例1）

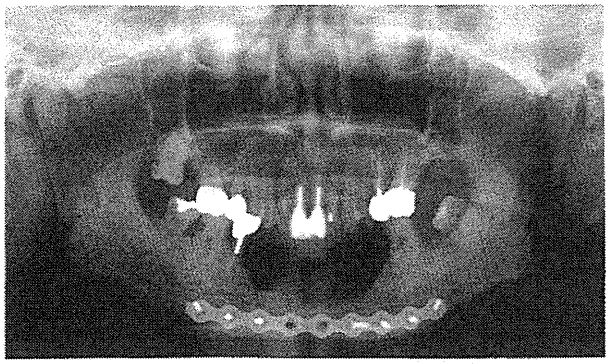

図2　初診時のレントゲン写真（症例1）

よび終了後における口腔粘膜炎の発症は認められなかった。

2）手術直前

プラークコントロールはおおむね良好に保たれており，口腔粘膜炎は認められなかった。手術前日に全顎的なスケーリングおよび歯面研磨（プラークフリー）を行った。

3）手術後

下顎骨区域切除により皮弁再建がなされていた。手術直後は含嗽が困難であり，残存歯のセルフケアが不可能であった。また，経口摂取をしていないことにより，口腔乾燥を認め，自浄作用の低下により口蓋や皮弁に痂皮の付着を多く認めた。そのため，メディカルスタッフによる口腔内清掃を継続して行った。すなわ

表2　手術直前の歯周組織検査結果（症例1）

上顎	頬側	2 2 3		1 1 2	2 2 1	1 1 1	1 1 1	1 2 2	3 1 1	3 2 3	3 2 1	1 1 1	1 1 1	2 1 1	2 2 2								
	口蓋側	3 2 6		2 2 3	2 2 2	2 2 3	2 2 3	2 2 2	3 2 3	3 3 3	3 3 2	2 2 3	3 2 3	3 3 3	6 2 3								
	動揺度	0		0	0	0	0	0	1	1	0	0	0	1	1								
歯式		8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8						
下顎	動揺度		0	0	0										0		0						
	舌側		2 3 2	2 2 2	2 2 2										2 2 2		2 2 2						
	頬側		1 1 1	1 1 1	1 1 2										1 1 1		2 2 2						

赤字はBOP(+)の部位を示す。

ち，歯科医師・歯科衛生士が1日1回歯ブラシ・歯間ブラシ・スポンジブラシを用いて，また，看護師が1日数回スポンジブラシを用いて歯や口腔粘膜の清拭を行った。皮弁周囲や咽頭部に貯留した唾液や痰は，適宜吸引を行った。術後12日目に飲水の許可がおりたため，セルフケアが可能となった。上顎残存歯は歯ブラシによるブラッシングを行い，下顎両側大臼歯はスポンジブラシによる清拭を行うよう指導した。その後も縫合部や皮弁周囲の清掃は困難であるため，歯科医師・歯科衛生士による口腔ケアを継続して行った。さいわい，創部からの感染や発熱，誤嚥性肺炎等の合併症は認められなかった。また，歯や歯肉に起因する有害事象は認められなかった。

症例2

患　者：64歳，男性

初診日：2013年4月

主　訴：喉が痛い

現病歴：2013年3月頃から喉の痛みを自覚していたものの，風邪だと思い込み放置していた。しかし，症状は消退しないため，同年4月に近くの耳鼻咽喉科を受診したところ，ファイバースコープにて左片側の咽頭に腫瘤を認めたため，当院耳鼻咽喉科へ紹介となった。下咽頭がん（T3N2bM0）との診断を受け，術前化学療法（ネダプラチンと5-フルオロウラシルの併用）と外科手術の適応となった。がん治療における口腔ケアの重要性を勧められ，当院予防歯科へ紹介となった。

全身既往歴：初診時の血液検査において，空腹時血漿グルコース（FPG）値が234 mg/dl，グリコヘモグロビン（HbA1c）値が6.7%であり，当院腎臓・糖尿病・内分泌内科にて2型糖尿病との診断を受けた。また，飲酒歴は日本酒を1日3〜4合，喫煙歴は1日20本×40年間である。

1．初診時現症

1）口腔内所見

現在歯数は上顎13本，下顎9本の合計22本であった。全顎的に歯根露出を認めた。また，27は全部鋳造冠による修復がなされていた。多数歯にわたって動揺が認められ，特に18および27の動揺度は3度であった。PCRは84.1%であり，全顎的な辺縁歯肉の発赤および腫脹を認めた。また，12，13，22，44より排膿を認めた。1歯6点法による平均PDは3.2 mmであり，BOP割合は75.0%であった（表3および図3）。

2）デンタルエックス線検査所見

全顎的に歯根の1/2〜1/3程度に及ぶ水平性および垂直性の歯槽骨吸収が認められた。特に18近心の歯槽骨吸収は著しく，また，44および46歯根周囲にび漫性の歯槽骨吸収が認められた（図4）。

3）口腔粘膜所見

特に異常は認められなかった。

4）血液検査値

初診時における白血球数は8000/μlであった。また，FPG値は234 mg/dl，HbA1c値は6.7%であった。

2．治療方針

化学療法および外科手術における口腔内感染源の除去は重要であるが，患者のプラークコントロールが不良であるため，まずセルフケアの向上が必要であると考えた。また，本患者は2型糖尿病に罹患しており，歯周病が悪化しやすい[3]ため，口腔内感染源の除去を徹底的に行い，術後も短い間隔で継続した歯周治療が必要であると考えた[4]。また，化学療法による口腔粘膜炎発症の可能性があるため，口腔粘膜のこまめな観察と消炎処置が必要であると考えた。

3．治療経過

1）術前化学療法中の経過

2型糖尿病に対しては，リナグリプチン（トラゼンタ®，日本ベーリンガーインゲルハイム株式会社，東京）の内服，食事療法，運動療法の適応となった。その結果，FPG値は118 mg/dlに低下した。

口腔内については，46部の歯槽骨吸収が著しく，動揺および咬合時痛を認めたため，抜歯の適応となった。化学療法に伴う骨髄抑制の可能性を考慮し，早期（化学療法開始当日）に抜歯を行った。また，これまでのセルフケアは1日1回（夕食後のみ）であり，プラークコントロールも不良であったため，口腔衛生管理の重要性について説明し，ブラッシングの習慣を含めた口腔清掃指導を行った。その結果，口腔清掃状態は改善した（PCR：84.1%→32.4%）。また，スケーリング，歯周ポケット内洗浄，排膿を認めた歯周ポケット内への薬剤（ペリオクリン歯科用軟膏®，サンスター株式会社，大阪）注入を行った。その結果，平均PDは2.8 mmに，BOP割合は27.0%に減少した（表4）。化学療法に伴う白血球数の減少はほとんど見られなかった。また，化学療法中および終了後における口腔粘膜炎の発症は認められなかった。

2）手術直前

手術直前のFPG値は173 mg/dlとやや増加していたが，HbA1c値は6.5%に低下していた。プラークコントロールはおおむね良好に保たれており，口腔粘膜炎は認められなかった。手術前日にプラークフリーを行った。

表3　初診時の歯周組織検査結果（症例2）

上顎	頬側	2	1	6							2	1	2	2	2	2	3	5	3	3	2	3	3	3	3	2	4	2	4	2	3	2	2	2	2	5	2	3	2	2	2	5	3	3	
	口蓋側	5	3	6							3	5	5	5	5	4	4	3	3	5	4	3	3	3	5	3	2	3	3	2	3	3	3	3	3	3	5	5	4	5	8	6	3	6	4	6	
	動揺度	3									1			0			0			1		1			1			0			0			1			2			3			
歯式		**8**		**7**		**6**		**5**		**4**		**3**		**2**		**1**		**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**	
下顎	動揺度					2		1		2		0		2				1		1		0		2									
	舌側					3	3	3	4	4	3	3	2	3	3	2	3	3	2	2	2	1	3	2	2	2	3	1	2	2	5	3												
	頬側					1	3	1	2	2	2	8	7	5	3	2	6	5	2	3			2	2	3	3	3	3	2	3	4	2	2												

赤字はBOP(+)の部位を示す。

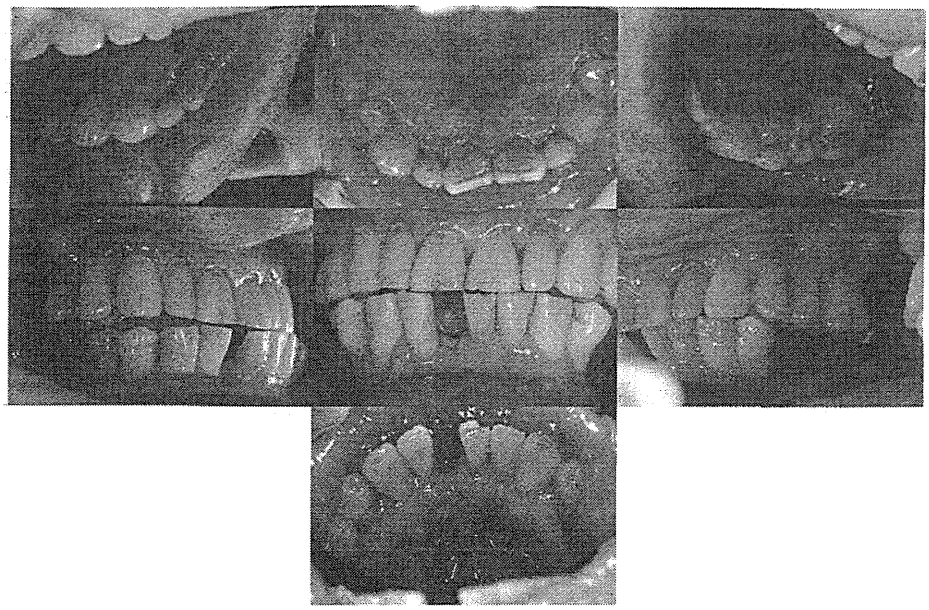

図3　初診時の口腔内状態（症例2）

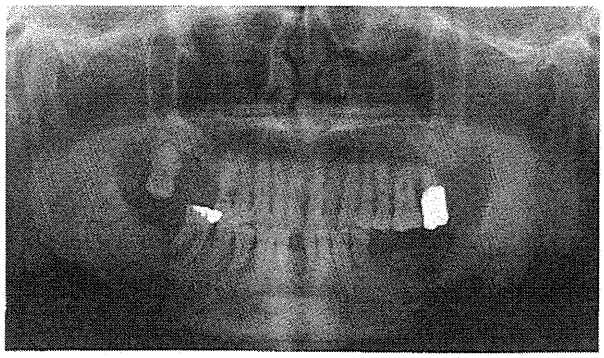

図4　初診時のレントゲン写真（症例2）

3）手術後

創部の口腔内への露出はなかったが，手術直後は嚥下が不可能であるため，経口摂取をしていないことによる口腔乾燥を認めた。また，自浄作用の低下により口蓋や皮弁に痂皮の付着を認めた。口腔衛生状態不良は誤嚥性肺炎のリスク因子となるため，体調にあわせてできるだけ頻回にセルフケアを行うよう指導した。あわせて，歯科医師・歯科衛生士・看護師が1日数回，歯ブラシ・歯間ブラシ・スポンジブラシを用いて口腔内清掃を行った。発熱，誤嚥性肺炎等の合併症は認められなかった。また，歯や歯肉に起因する有害事象は認められなかった。

表4　手術直前の歯周組織検査結果（症例2）

上顎	頬側	3	3	6							1	1	3	2	3	2	3	5	3	2	3	3	3	4	2	2	3	2	2	2	1	1	4	2	3	2	1	2	4	2	2	4	3	
	口蓋側	3	3	9							4	5	5	4	5	5	3	3	4	4	3	3	4	3	4	4	2	2	3	3	3	3	2	4	3	3	4	4	4	4	7	3	3	5	4	4	
	動揺度	1																																						1		3			
歯式		**8**		**7**		**6**		**5**		**4**		**3**		**2**		**1**		**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**	
下顎	動揺度							1		2				1										2									
	舌側							3	3	3	2	2	2	2	2	2	2	2	2	1	1	1	2	1	1	1	1	4	4															
	頬側							2	2	2	6	6	6	3	2	3	3	1	2			1	1	2	2	2	3	3	2	1	2	2												

赤字はBOP(+)の部位を示す。

考　察

頭頸部がんは他部位のがんと異なり，細菌の多い口腔が領域に含まれるのが特徴である。したがって，細菌感染による合併症の発症リスクが高い[5]。頭頸部がん治療に対する口腔ケアは合併症の予防・軽減に有効である。大田らは，同一術者による頭頸部がん再建手術症例において，口腔ケアを行った群の術後合併症の発生率（16.1%）は，口腔ケアを行わなかった群の発生率（63.6%）に比べて統計学的に有意に少なかったと報告している[6]。

術後は患者自身による口腔内清掃が困難となる。また，口腔からの食物摂取が不可能であるため，自浄作用が低下する。さらに，口唇閉鎖が困難となる症例も多く，口腔内が乾燥しやすい。そのため，術後において口腔内細菌が増加すると考えられる。術前までに歯科医師・歯科衛生士がスケーリング・歯面研磨を行い，プラークをいったん完全に除去しておくと，その後は清拭程度の簡単な口腔ケアでもプラークの再付着は生じにくく，看護師による口腔ケアを簡略化することができる[7]。このことから，術前におけるプラークフリーが重要視されている。

今回の症例では，2症例とも術前のプラークコントロールが不良であった。また歯周状態も不良であった。そのため，がん治療開始前より歯科医師・歯科衛生士が口腔内清掃の重要性について指導し，セルフケアの向上に努めた。その結果，術前までに口腔清掃状態は改善し，歯周状態もおおむね改善されていた。さらに，術前のプラークフリーを行うことで口腔内細菌量が減少し，術後も口腔内細菌量をできるだけ抑えることができた結果，口腔内合併症が発生しなかったと考えられる。

化学療法や放射線治療によりがん細胞が死滅する。しかし，同様に細胞周期の早い口腔粘膜もダメージを受け，口腔粘膜炎を発症する。発症の機序としては，まず，化学療法や放射線治療により細胞内において活性酸素が発生し，組織破壊が起きる。そして，口腔粘膜に潰瘍が生じると，細菌のリポ多糖が粘膜下層に侵入し，マクロファージによって多くのサイトカインが産生され，炎症が増大する[8]。口腔粘膜炎は化学療法の42%，頭頸部領域への放射線治療の38%に発症するとの報告がある[9,10]。特に，フッ化ピリミジン系，メトトレキサート，アントラサイクリン系の抗がん剤において口腔粘膜炎の頻度が高い[11]。口腔粘膜炎を発症すると，激しい痛みを伴うため，栄養摂取が困難となるため，Quality of life（QOL）の低下[12]や入院日数や医療費の増加をもたらす[13]。したがって，口腔粘膜炎の予防が重要となる。造血幹細胞移植が必要な血液がん患者に対して，パリフェルミン（遺伝子組換え型ヒトケラチノサイト成長因子で，粘膜細胞の成長を促進する作用がある）を投与すると口腔粘膜炎の重症化を抑えるとの報告[14]があるが，有効性や安全性については不明である。また，口腔粘膜炎に対する効果的な予防法に関するプロトコールは確立されていないのが現状であり，感染予防のための口腔内清潔保持，口腔内保湿を基本とした対症療法が一般的である。本症例ではどちらもフッ化ピリミジン系である5-フルオロウラシルを使用しており，口腔粘膜炎発症の可能性があった。そのため，治療開始前より口腔ケアの方法について説明し，患者の協力もあり，口腔粘膜炎を発症することなく，化学療法を完遂することができた。

化学療法により骨髄抑制が生じ，好中球が減少することで免疫力の低下を招く。その結果，口腔内細菌が増加しやすい。また，唾液腺が照射野に含まれる放射線治療の場合，唾液分泌減少が著明に生じ，口腔乾燥によって口腔内細菌の増加が起きる。したがって，口腔内清潔保持のためには，化学療法・放射線治療開始前より口腔内清掃を行うとともに，セルフケア方法を指導することが重要である。普段使用している歯ブラシでは口腔粘膜に傷をつけ，口腔粘膜炎の重症化の可能性があるため，軟毛タイプの歯ブラシを勧めているが，その反面，清掃能力が低下するため，歯ブラシの当て方や力加減について注意深く指導する必要がある。また，口腔乾燥に対しては，刺激性のない保湿剤の使用を積極的に使用し，常に口腔内を湿潤に保つ必要がある。さらに，抗炎症作用をもつ含嗽剤や軟膏の使用により，口腔粘膜炎の重症化を予防する必要がある。

大田らの報告[6]によると，頭頸部がんの術後合併症に影響を与える因子は，口腔ケアの有無と術前の糖尿病の有無である。したがって，症例2のように，術前より適切な血糖コントロールを行うことは，口腔内状態のみならず，術後の全身状態の安定にも寄与していると考えられる。

頭頸部がん治療における口腔内の合併症は治療中のQOLを低下させるが，患者はそれをイメージできていないことが多い。また，がんの告知を受けて，メディカルスタッフの説明が頭に入らないケースもある。口腔内の合併症に関してビデオを用いた患者教育は有効であるとの報告[15]があり，当院においてもパンフレットを用いて視覚的な説明を行っている。頭頸部がん治療における口腔ケアは，単にメディカルスタッフが口腔内清掃を行うという受身的な治療ではない。がんの

治療方針をもとに予想される合併症を考え，患者にとって簡単かつ効果的なセルフケア方法を提案し，患者とメディカルスタッフが一体となって合併症を予防し，がん治療に専念し，がんを克服することが重要であると考えられる。

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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-fluorouracil, *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.