PERGAMON

European Journal of Cancer 37 (2001) 1994–2002

European Journal of Cancer

www.ejconline.com

Decrease of duration and symptoms in chemotherapy-induced oral mucositis by topical GM-CSF: results of a prospective randomised trial

M. Hejna [a], W.J. Köstler [a], M. Raderer [a], G.G. Steger [a], T. Brodowicz [a], W. Scheithauer [a], C. Wiltschke [a], C.C. Zielinski [a,b,*]

[a] *Department of Medicine I, Division of Oncology, University Hospital, 18–20 Waehringer Guertel, A-1090 Vienna, Austria*
[b] *Department of Medicine I, and Ludwig Boltzmann Institute for Clinical Experimental Oncology, Vienna, Austria*

Received 15 November 2000; received in revised form 16 February 2001; accepted 27 March 2001

Abstract

We have conducted a prospective controlled randomised clinical study testing for the efficacy of topical GM-CSF (molgramostim), as compared to the combined topical use of an antiseptic agent (povidone-iodine) and amphotericin B (AA) in patients with chemotherapy-induced mucositis World Health Organization (WHO) grades I–III. 31 patients (17 females, 14 males) developing oral mucositis following the administration of 5-fluorouracil (5-FU)-based chemotherapy were entered into the present trial. 15 patients were randomised to receive GM-CSF mouthwashes, whereas 16 patients were randomised into the control arm to receive AA. Reported history ($P=0.6109$) and grading of oral mucositis (2.1 ± 0.7, respectively; $P=0.9867$) were balanced and equally distributed between the two groups. The mean size of lesions of oral mucositis was 1.5 ± 0.6 cm (range: 0.7–2.5 cm) in the GM-CSF group and 1.2 ± 0.5 cm (range: 0.5–2.5 cm) in the AA group ($P=0.08$), respectively. The mean number of oral mucositis lesions was 1.9 ± 1.1 (range: 1–4) in the GM-CSF group and 2.1 ± 1.2 (range: 1–4) in the AA group ($P=0.63$), respectively. None of the patients had previously received colony stimulating factors either topically or systemically. Treatment for oral mucositis was initiated on day 2.7 ± 1.2 (range: day 1–8) after onset of symptoms in the GM-CSF group and on day 1.8 ± 1.4 (range: day 1–3; $P=0.11$) in the AA group. The topical application of GM-CSF resulted in a significantly shorter duration and quicker resolution of oral mucositis, as compared to AA including both, pretreatment plus treatment periods (5.3 ± 2.5 versus 8.1 ± 1.5 days; $P=0.0008$) as well as the necessary duration of treatment needed until complete remission of lesions (2.8 ± 0.7 versus 6.3 ± 1.1 days; $P<0.0001$). A systemic effect of topical GM-CSF upon the number of peripheral blood leukocytes or granulocytes was excluded. We conclude that the topical application of GM-CSF by mouthwash significantly abbreviated the duration and relieved patients from symptoms of chemotherapy-induced mucositis and was superior to the topical application of AA.

Keywords: Oral mucositis; Chemotherapy; GM-CSF; Topical

1. Introduction

Oral mucositis and the associated emergence of inflammatory-like changes at various locations of the oral cavity has been reported to complicate the course in up to 40% of patients receiving standard cytotoxic chemotherapy particularly including 5-fluorouracil (5-FU)-based regimens [1,2] and 76% of bone morrow transplant recipients following high-dose treatment [3]. While rarely life-threatening, the discomfort and pain associated with oral mucositis may impair oral intake of fluids and calories resulting in anorexia, cachexia, dehydration and overt malnutrition [4]. Such complications related to oral mucositis may in turn lead to costly hospitalisations due to the necessity of the administration of parenteral nutrition and fluid replacement and narcotics for pain control. In addition to the obvious negative impact on the patient's quality of life as a result of pain [5], the presence of mucositis-associated lesions may necessitate interruption of treatment, reduction of

* Corresponding author. Tel.: +43-1-40400-4445; fax: +43-1-40400-4452.
E-mail address: christoph.zielinski@akh-wien.ac.at (C.C. Zielinski).

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00132-0

dose of chemotherapeutic agents and affect the patients' compliance with other prescribed medications.

In the past, various strategies have been applied for both prevention and treatment of mucositis. Early attempts have included oral cryotherapy [6] as well as chlorhexidin mouthwashes [6] in the preventive setting. Currently, the range of medications tested for mucositis developing after 5-FU-based cytotoxic treatment is extensive and includes topical antimicrobials, vitamins, inflammatory modifiers, palliative rinses, amino acid supplementation, cryotherapy and laser treatment [6]. Moreover, good oral hygiene seems to play a crucial part in the prevention of mucositis and can be achieved manually and/or by means of antiseptic or antifungal agents directed against *Candida albicans* [7]. The latter approach has been shown to result in a reduction of both frequency and severity of infections [8]. A more modern approach in the treatment of mucositis relies on the fact that the development of oral mucositis might also be associated with deteriorated hematological status in patients undergoing myeloablative treatment [9] and resolve coinciding with neutrophil recovery [10]. These observations have resulted in the successful parenteral administration of haematopoetic growth factors including granulocyte-(G-CSF) and granulocyte/macrophage-colony stimulating factor (GM-CSF) for oral mucositis occurring in correlation with myeloablation [9] or therapy-associated [10] and congenital [11] neutropenia. However, G-CSF and GM-CSF may also directly induce proliferation of endothelial cells and keratinocytes [12]. Thus, topical application of GM-CSF has been shown to accelerate healing of infected wounds in a number of animal models [13] as well as in humans where it has been reported to facilitate healing of decubital [14] and chronic leg ulcers [15] as well as Kaposi sarcoma lesions [16]. The efficacy of systemic and topical application of GM-CSF or G-CSF in oral mucositis in shortening duration and decreasing symptoms [17] irrespective of reconstitution of regular neutrophil counts has been suggested by anecdotal reports [18], uncontrolled clinical trials [19,20] and also by one randomised placebo-controlled trial which used G-CSF in patients with high-grade lymphoma following chemotherapy [21].

Despite some scattered encouraging, yet uncontrolled, reports on the efficacy of various treatment modalities of chemotherapy-induced mucositis [1,2], there is currently no established standardised treatment for this disorder. This lack of consistency of therapeutic interventions is further complicated by the absence of a standardised assessment scale which would permit clinical evaluation and allow for a direct comparison of various approaches [22]. Thus, treatment for oral mucositis grades I–III [defined by the World Health Organization's (WHO) scale of the National Cancer Institute's (NCI) Common Toxicity Index (CTI)] varies between institutions, although it mainly consists of the topical administration of antiseptic and antifungal agents and — in case of severe pain — topical anaesthetics [23]. However, conflicting data concerning the efficacy of chlorhexidine mouth rinse in the prevention of chemotherapy-induced oral mucositis have been produced [24], and the use of the substance has been reported to induce mouthwash-associated discomfort thus negating its potential benefit [25]. Moreover, the topical antiseptic effect of chlorhexidine upon colonisation of the oral mucosa with Candida species has also produced controversial results [24].

The considerations outlined above have led us to design a prospective controlled randomised clinical study testing the efficacy of topical GM-CSF (molgramostim) compared with the topical use of both povidone-iodine as an antiseptic agent of proven efficacy, [26] yet low irritating potential, and amphotericin B (AA) in patients with chemotherapy-induced mucositis WHO grades I–III. Objective and subjective reduction of extent and symptoms from chemotherapy-induced oral mucositis constituted the primary study goal. We report that topical application of GM-CSF resulted in an early, highly significant abbreviation of the disease as well as in a highly significant improvement of symptoms of chemotherapy-induced oral mucositis, as compared with AA which resulted in the termination of the trial with a relatively low number of patients recruited due to ethical reasons. This effect was independent from peripheral leukocyte or granulocyte counts. We conclude, therefore, that the topical application of GM-CSF presently constitutes treatment of choice for patients with chemotherapy-induced oral mucositis.

2. Patients and methods

2.1. Eligibility criteria

Patients with grade I–III oral mucositis (as defined by the WHO's scale of the NCI's CTI) following 5-FU-based chemotherapy were eligible for the study. Patients were required to be $\geqslant 19$ years of age, have the ability to read and understand the locally spoken language (German) and present with WHO performance status of <3. Patients with a history of adverse reactions to G-CSF, GM-CSF or iodine and with severe concomitant diseases including hyperthyroidism and/or dermatitis herpetiformis Duhring were ineligible, as were individuals with the need for systemic G-CSF or GM-CSF treatment for febrile neutropenia. Patients who had undergone radiotherapy of head and neck were eligible, if at least 6 weeks had elapsed since termination of therapy and the resolution of acute toxic effects of treatment. The study protocol was approved by the local ethical

committee and all patients gave informed consent according to institutional guidelines before study entry.

2.2. Treatment plan

Patients received a data collection form containing a table for recording the symptoms of oral mucositis (Grading: 0. None, 1. Mild soreness, mild dysphagia, solid diet possible, 2. Moderate soreness, moderate dysphagia, soft diet or liquid diet possible, 3. Severe pain, severe dysphagia, liquids only) and their duration during days 1–10 (=functional oral mucositis scores given by patients). Patients were asked to place a mark corresponding to the degree of oral mucositis for each day at the begin of treatment (= day 1).

After obtaining the patient's subjective assessment, clinical examination was performed by clinical examination and independent rating of severity of mucositis by two investigators independently and the ascertainment of fulfilment of eligibility criteria, randomisation to treatment arm A or B was performed without further stratification and according to a balanced block randomisation procedure by a third investigator who had no information about rating of severity preceding or current results of the two available treatment modalities within the present trial. Physicians were not blinded, but patients were as to the efficacy of any of the chosen regimens (arm A or arm B).

Arm A consisted of topical GM-CSF (Leucomax®, molgramostim, Novartis, Basel, Switzerland) administered as a mouthwash thrice daily. One mouthwash consisted of 400 μg molgramostim dissolved in 250 ml of water. Patients were instructed to wash their mouths with 25 ml of this solution and keep the solution in their mouths for 3 min without swallowing. Subsequently, patients were allowed to rinse and instructed to repeat the procedure 10 times within 30 min. The intervention was performed thrice daily in an identical way and at an identical time during subsequent days.

Arm B consisted of topical therapy according to the AA schedule representing six daily mouthwashes with 4 ml of povidone-iodine antiseptic agent (Betaisodona Mund-Antiseptikum®, Mundipharma, Limburg/Lahn, Germany) in 125 ml of water. As with arm A, patients were instructed to wash their mouths with this solution and to keep it in their mouths altogether for 3 minutes without swallowing; subsequently, patients were allowed to rinse. The mouthwashes were carried out every day in an identical way and at the identical time. In addition, patients received four daily tablets for the topical administration of amphotericin B (Ampho-Moronal-Lutschtabletten® 10 mg, Bristol-Myers Squibb, München, Germany). All patients with oral mucositis exceeding grade II were offered topical lidocain (Xylocain-viscös oral 2%®, Astra, Wedel, Germany) six times daily, patients with mucositis grades I or II only upon the patients' request for pain control.

Both treatment modalities were stopped in case of complete response, but continued for another period of 3 days in the case of improvement without the complete resolution of symptoms and/or lesions, respectively. Treatment was discontinued in case of severe side effects or upon the patients' request. In the case of treatment failure for >6 days, patients were taken off study and treated at their physician's discretion.

2.3. Evaluation methods

Evaluation of response of oral mucositis to topical GM-CSF or AA was done in intervals of 3 days. Endpoints of the study were objective and subjective response, time to response, duration of oral mucositis and duration of treatment in both arms.

Haematological evaluations were carried out weekly from the start of inclusion in the study until complete recovery from oral mucositis. The use of analgesics for oral and/or tumor-associated pain was recorded for all patients. Possible side-effects of GM-CSF including bone pain, headache, nausea, vomiting, diarrhea and fever were monitored during treatment. All patients were asked for their oral hygiene/care practices, their smoking status and their ingestion of alcohol. Oral hygiene/care practices were defined as the frequency of brushing and flossing and the time elapsed since the last professional cleaning of teeth as well as the last dental visit by study participants. Smoking and also ingestion of alcohol during the time of treatment as well as treatment compliance were recorded.

2.4. Statistical analysis

Data are presented as mean standard deviation (range). Statistical significance was assessed using Student's *t*-test and Chi square test. In order to assess the equally balanced treatment groups, correlation analysis according to Pearson was performed. All statistical calculations were performed with the BMDP-PC program package using a significance level of <0.05. *P* values are quoted two-tailed.

3. Results

3.1. Study population

Between March 1998 and June 1999, 31 patients (17 females, 14 males) who had developed oral mucositis following the administration of chemotherapy for different tumour entities (see below) were entered into the present trial at the University Hospital of Vienna, Austria. 15 patients were randomised to receive GM-CSF

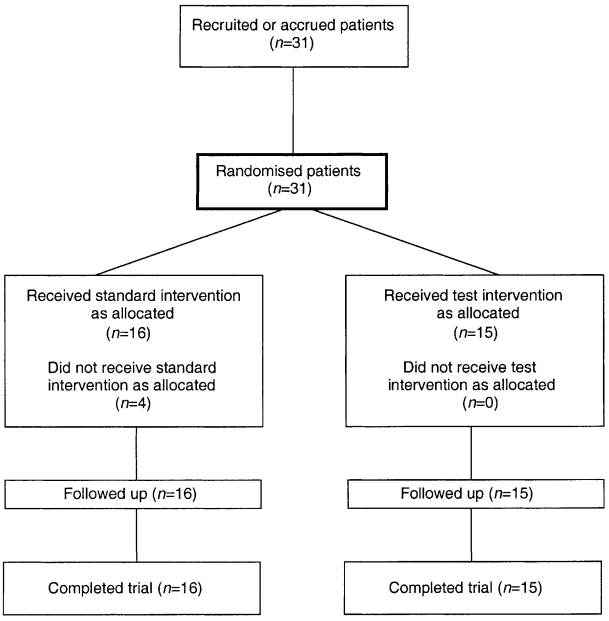

Fig. 1. Flow chart of the progress of patients through the trial.

mouthwashes, whereas 16 patients were randomised into the control arm to receive AA (Fig. 1). The median age of patients in the GM-CSF group was 58 years (range: 39–77 years) and in the AA group 73 years (range: 48–80 years). The median WHO performance status in the GM-CSF group was 0.73 (range: 0–2) and in the AA group 1.71 (range: 0–2), respectively. 17 patients (6 GM-CSF/11 AA) received chemotherapy for colorectal carcinoma, 9 patients (4 GM-CSF/5 AA) for gastric carcinoma, 3 patients (randomised to receive topical GM-CSF) for breast cancer and 1 patient for pancreatic cancer (GM-CSF) and cholangiocellular carcinoma (GM-CSF), respectively. History of previous chemotherapy-associated mucositis was present in 9 patients from the GM-CSF-arm and in 11 patients from the AA-arm, respectively. All study patients were treated with either GM-CSF or AA until the complete remission of oral lesions.

3.2. Patients

3.2.1. Characteristics and features of mucositis

Patient characteristics are shown in Table 1. Moreover, Table 1 also shows characteristics pertinent to the present topic including smoking habits, the ingestion of alcohol, tooth status and oral hygiene and characteristics, history and grading of mucositis. Although oral hygiene tended to be better in the GM-CSF group, the time elapsed since the last professional cleaning of teeth, the last dental visit by study participants as well as the tooth status were balanced between both study groups. In contrast, smoking and ingestion of alcohol (only wine, no hard liquor) were more frequent in the AA group. Reported history ($P=0.6109$) and grading of oral mucositis (2.1 ± 0.7; $P=0.9867$), respectively, were balanced and equally distributed in the two groups.

3.2.2. Occurrence of oral mucositis relative to chemotherapy dose and cytotoxic treatment

Oral mucositis occurred after 2.4 ± 1.7 (range: 1–6) chemotherapy cycles in the GM-CSF group and after 4.9 ± 3.4 (range: 1–16) in the AA group, respectively. As can be seen in Table 1, all patients included had undergone 5-FU-based therapy. The mean dosage of 5-FU applied per month was 1.665 ± 369 mg/m^2 (range: 1.200–2.250 mg/m^2) in the GM-CSF group and 1.530 ± 632 mg/m^2 (range: 360–2.250 mg/m^2; $P=0.4763$) in the AA group, respectively. The mean dosage of leucovorin applied per month was 339 ± 390 mg/m^2 (range: 0–1.000 mg/m^2) in the GM-CSF group and 159 ± 139 mg/m^2 (range: 0–600 mg/m^2; $P=0.0731$) in the AA group, respectively. In the GM-CSF group, 9 patients had first-line, 5 second-line and 1 third-line chemotherapy, whereas all patients had first-line chemotherapy in the AA group.

3.2.3. Size and location of mucositis lesions

Table 2 presents the number and sizes of mucositis lesions including the allocation to treatment arms. The mean size of lesions of oral mucositis was 1.5 ± 0.6 cm (range: 0.7–2.5 cm) in the GM-CSF group and 1.2 ± 0.5 cm (range: 0.5–2.5 cm) in the AA group ($P=0.0848$), respectively. The mean number of oral mucositis lesions was 1.91.1 (range: 1–4) in the GM-CSF group and 2.1 ± 1.2 (range: 1–4) in the AA group ($P=0.6264$), respectively.

3.2.4. Concomitant treatment

The following concomitant analgesic medication was given: In the group of patients receiving topical GM-CSF, 1 patient received 400 mg tramadol daily and another 240 mg dihydrocodein daily, whereas in the group of patients receiving AA, 1 patient received 200 mg tramadol daily, although according to study protocol offered, none of the patients actually used local lidocain for analgesia of oral mucositis. The patients using tramadol or dihydrocodein had oral mucositis grade III (3 out of 8 patients). In both treatment arms, no patient had to be hospitalised for institution of additional supportive measures.

3.3. Treatment of mucositis

3.3.1. Initiation of treatment

Treatment for oral mucositis was initiated on day 2.7 ± 1.2 (range: day 1–8) of mucositis in the GM-SCF group and on day 1.8 ± 1.4 (range: day 1–3; $P=0.1086$) in the AA group (Table 3).

Table 1
Characteristics of patients included into treatment arms of topical GM-CSF versus topical combined therapy with antiseptic and amphotericin B (AA) for chemotherapy-induced oral mucositis

	GM-CSF arm	AA arm	*P* value
Number of patients	15	16	
Age, years (median/range)	58 (39–77)	73 (48–80)	0.0095
Sex (*n*)			
Female	10	7	
Male	5	9	
WHO performance status (median)	0.73	1.71	0.0032
Grade 0	8	3	
Grade I	3	0	
Grade II	4	10	
Grade III	0	3	
Diagnosis (*n*)			
Colorectal cancer	5	11	
Gastric cancer	4	5	
Pancreatic cancer	1	0	
Breast cancer	3	0	
Cholangiocellular cancer	1	0	
Smoking during therapy (*n*)	1	7	0.0184
Ingestion of alcohol (*n*)	1	5	0.0834
Medication for tumour pain (*n*)	2 (tramadol 400 mg/day and dihydrocodein 240 mg/day, respectively)	1 (tramadol 200 mg/day)	
Tooth status (*n*)			
Healthy	14	15	
Not healthy	1	1	
No denture	7	2	
Partial denture	3	4	
Complete denture	5	10	
Oral hygiene			
Pretentious	14	5	0.0004
Average	1	11	0.0007
No oral hygiene	0	0	
Professional cleaning within the last 6 months (*n*)	2	2	
Time since the last dental visit in months (median/range)	6.0±2.8 (1–12)	7.5±4.5 (1–18)	0.2357
Chemotherapy			
First-line	9	16	
Second-line	5	0	
Third-line	1	0	
Chemotherapeutic agents (*n*) administered in mg/m^2 per month Mean±standard deviation (range)			
5-fluorouracil (15 versus 16 patients)	1.665.0±369.4 (1.200–2.250)	1.529.7±630.6 (360–2.250)	
Leucovorin (12 versus 15 patients)	339.3±389.5 (0–1000)	159.1±139.3 (0–600)	0.0731
Mitomycin C (1 versus 3 patients)	0.4±1.5 (0–6)	1.1±2.4 (0–6)	
Etoposide (4 versus 4 patients)	89.0±154.7 (0–360)	74.7±133.9 (0–325)	
Cisplatin (0 versus 3 patients)	0	9.4±20.2 (0–50)	
Oxaliplatin (1 versus 0 patients)	5.7±21.9 (0–85)	0	
Cyclophosphamide (3 versus 0 patients)	242.3±501.7 (0–1235)	0	
Methotrexate (3 versus 0 patients)	16.0±33.1 (0–80)	0	
Gemcitabine (1 versus 0 patients)	66.7±258.2 (0–1.000)	0	
Irinotecan (1 versus 0 patients)	6.7±25.9 (0–100)	0	
Reported mucositis history (*n*)	9	11	0.6109
Oral mucositis occurrence after chemotherapy cycle no. Mean±standard deviation (range)	2.4 ±1.7 (1–6)	4.9±3.4 (1–16)	0.0167
Oral mucositis occurrence after 5-FU application in days Mean±standard deviation (range)	4.3±1.2 (2–6)	3.8±1.4 (2–7)	0.2823

(*Continued on next page*)

Table 1 (*continued*)

	GM-CSF arm	AA arm	*P* value
Oral mucositis assessed by investigators according to the Common Toxicity criteria (CTC) at baseline			
Grade I	3	3	
Grade II	8	9	
Grade III	4	4	
Mean grade ± standard deviation	2.1 ± 0.7	2.1 ± 0.7	0.9867
Size of lesions: mean ± standard deviation (range)	1.45 ± 0.58 (0.7–2.5)	1.22 ± 0.45 (0.5–2.5)	0.0847
Number of lesions: mean ± standard deviation (range)	1.87 ± 1.06 (1–4)	2.07 ± 1.16 (1–4)	0.6263

3.3.2. *Efficacy of treatment*

Topical application of GM-CSF resulted in a significantly shorter duration and quicker resolution of oral mucositis including both pretreatment plus treatment periods ($P = 0.0008$) as well as the necessary duration of treatment needed until complete remission of lesions ($P < 0.0001$), as compared to AA, respectively (Table 3). Thus, pretreatment plus treatment periods necessary to achievement of complete response were 5.3 ± 2.5 days (range: 2–11 days) in the GM-CSF group and 8.1 ± 1.5 days (range: 6–11 days) in the AA group ($P = 0.0008$). Necessary duration of treatment for the achievement of complete remission was 2.8 ± 2.7 days (range: 2–4 days) in the GM-CSF group, whereas it was 6.3 ± 1.1 days (range: 5–8 days) in the AA group ($P < 0.0001$). GM-CSF mouthwashes were well tolerated without any oral discomfort or systemic side-effect. Oral mucositis did not progress under topical treatment with either GM-CSF or AA.

Table 2
Location of oral mucositis

Location of oral mucositis	Number of lesions		
	Lesion size (x)		
	$x < 1$ cm	1 cm $\leqslant x < 2$ cm	2 cm $\leqslant x < 3$ cm
Upper lip			
GM-CSF	0	3	0
AA	1	4	0
Lower lip			
GM-CSF	0	4	0
AA	1	2	0
Right cheek			
GM-CSF	1	2	2
AA	0	0	2
Left cheek			
GM-CSF	0	2	1
AA	0	5	1
Soft palate			
GM-CSF	0	2	2
AA	2	5	0
Hard palate			
GM-CSF	0	2	3
AA	0	5	1
Right ventral and lateral tongue			
GM-CSF	2	1	0
AA	0	1	0
Left ventral and lateral tongue			
GM-CSF	0	1	0
AA	1	1	0
Floor of mouth			
GM-CSF	0	0	0
AA	0	1	0

3.3.3. *Efficacy of treatment according to functional scores assessed by patients*

The mean grade of oral mucositis as assessed by the investigators according to CTC at baseline was well balanced and 2.1 ± 0.7 in both groups (Table 4). The mean grade of functional oral mucositis judged by patients at baseline was 1.9 ± 0.8 in the GM-CSF group and 2.3 ± 0.5 in the AA group ($P = 0.1628$). In terms of efficacy of treatment, Table 4 demonstrates that the mean grade of functional oral mucositis assessed by patients on day 3 of treatment was 0.9 ± 0.8 (range: 0–2) in the GM-CSF group and 2.1 ± 0.7 (range: 1–3) in the AA group ($P = 0.0004$) with no statement given by 2 patients from the AA group. Moreover, the mean grade of functional oral mucositis judged by patients on day 6 of treatment was 0.3 ± 0.7 (range: 0–2) in the GM-CSF group and 0.90.7 (range: 1–3) in the AA group ($P = 0.0194$). Finally, improvement of symptoms by one functional oral mucositis score as judged by patients occurred on day 2.8 ± 0.7 (range: day 2–4) in the GM-CSF group and on day 4.1 ± 1.0 (range: day 2–6) in the AA group ($P = 0.0011$) after starting treatment.

3.3.4. *Correlation of physicians' judgment of mucositis with patients' functional oral mucositis score*

Objective assessment of mucositis done by physicians correlated very closely with subjective functional oral mucositis scores given by patients in general ($r = 0.6156$; $P = 0.0004$), as well as those randomised to treatment arms with GM-CSF ($r = 0.6438$; $P = 0.0096$) and AA ($r = 0.7246$; $P = 0.0034$), respectively.

3.4. Haematological analyses

In order to exclude a systemic effect of topical GM-CSF application, peripheral blood counts before and after treatment were monitored in both groups. Results of these analyses are shown in Table 3. Clearly, no significant differences in peripheral blood leucocyte and granulocyte counts were observed either between the two treatment groups (i.e. patients receiving topical GM-CSF or AA, respectively) or subsequent to either treatment modality (Table 3).

4. Discussion

Oral mucositis has been described to develop in up to 40% of patients with malignant disorders as consequence of direct or indirect toxicity exerted by standard chemotherapy including 5-FU-based regimens [1,2]. This aspect gains additional importance in the scenario of high-dose chemotherapy followed by bone-marrow transplantation where the incidence of oral mucositis has been reported to be 76% [3]. Apart from 5-FU, other also widely used cytotoxic agents, including methotrexate, purine antagonists, doxorubicin and also liposomal doxorubicin, hydroxyurea and procarbacine [3], have been associated with the occurrence of oral mucositis, indicating the necessity for the development of appropriate treatment. Contrary to these facts and despite considerable advances in the supportive treatment of patients with malignant disorders, no standardised therapy for oral mucositis has been defined as yet.

Underlying causes of oral mucositis include the rapid turnover of cells of the oral cavity, immunosuppression and resulting colonisation with potentially pathogenic infectious agents [23], including primarily gram-negative organisms including klebsiella, serratia, enterobacter, *Escherichia coli*, pseudomonas and proteus as well as *C. albicans* [7]. Thus, treatment concepts of oral mucositis have mainly concentrated on the control of infection resulting in the topical institution of antiseptic and antifungal agents complemented by anesthetics for local analgesia [23]. However, only conflicting and controversial data have been published on the efficacy of various drug combinations for both, prevention [11] and treatment [24]. This lack of options has led us to conduct the present study using the AA arm for control. The selection of best supportive care for chemotherapy-induced oral mucositis was complicated by observations of further discomfort and alteration of taste induced by the widely used agent chlorhexidine [25]. Therefore, and under the consideration of an already problematic local

Table 3
Efficacy of treatment upon duration of oral mucositis and peripheral leukocyte and granulocyte counts

	GM-CSF arm	AA arm	*P*-value
Initiation of treatment for oral mucositis after occurrence on day	2.7 ±1.2 (1–8)[a]	1.8±1.4 (1-3)[a]	0.1086
Duration of oral mucositis (pretreatment plus treatment period)	5.3±2.5 (2–11)[a]	8.1±1.5 (6-11)[a]	0.0008
Duration of therapy of oral mucositis until complete remission	2.8±0.7 (2–4)[a]	6.3 ±1.1 (5–8)[a]	<0.0001
Leukocytes/mcl (median/range)			
Before treatment	7.400 (3.150–16.500)	6.750 (3.400–9.800)	0.7060
After treatment	4.650 (1.700–13.790)	6.100 (3.200–10.400)	0.4115
Leukocytes before versus after (*P*)	*P* = 0.0724	*P* = 0.5240	
Granulocytes/mcl (median/range)			
Before treatment	3.660 (1.900–13.600)	4.350 (1.500–6.400)	0.5937
After treatment	2.540 (600–11.250)	5.360 (3.400–7.200)	0.5111
Granulocytes before versus after (*P*)	*P* = 0.6780	*P* = 0.2214	

[a] Given as mean ±standard deviation (range) of days.

Table 4
Functional oral mucositis scores given by patients

	GM-CSF arm	AA arm	*P*-value
Functional oral mucositis scores given by patients at baseline[a]			
Grade I	5	0	
Grade II	6	10	
Grade III	4	4	
Mean grade±standard deviation	1.9±0.8	2.3±0.5	0.1628
Functional oral mucositis scores given by patients on day 3 of therapy[a]	0.9±0.8 (0–2)[b]	2.1±0.7 (1–3)[b]	0.0004
Functional oral mucositis scores given by patients on day 6 of therapy[a]	0.3±0.7 (0–2)[b]	0.9±0.7 (0–2)[b]	0.0194
Improvement of symptoms (at least one WHO grade) given by patients on day[a]	2.8±0.7 (2–4)[b]	4.1±1.0 (2–6)[b]	0.0011

[a] No statement made by 2 patients from the AA group.
[b] Mean grade ±standard deviation (range).

situation, we have preferred the application of an iodine-based antiseptic of proven efficacy yet neutral concerning the induction of pain or changes in taste. Under these considerations as well as in order to control the colonisation with Candida species, the local use of the iodine-based antiseptic was combined with the simultaneous application of amphotericin B (abbreviated as AA) in a controlled manner. We now report the results of a randomised trial testing the efficacy of topical GM-CSF compared with the local application of AA in patients with chemotherapy-induced oral mucositis. The studied population was well balanced for underlying malignant disorders, cytotoxic treatment and grades of oral mucositis. In comparison with AA, topical application of GM-CSF led to a significant decrease in the duration of oral mucositis, duration of necessity of treatment and — in parallel — a significant decrease of mucositis-associated symptoms measured by functional oral mucositis. Due to the complexity of the disorder and its major impact upon the patients' well-being, results of the current study were closely monitored and — consequently — both randomisation as well as recruitment of patients stopped for ethical reasons at the reported level of significance despite the relatively low number of patients included in the protocol.

Despite the balance between the two arms concerning a series of aspects including characteristics of the underlying disease, cytotoxic treatment and oral mucositis, patients experiencing significant benefit from GM-CSF had significantly larger lesions of oral mucositis and a longer history of application of chemotherapy. While patients in the AA group were found to have a higher consumption of cigarettes and a higher ingestion of alcohol, neither of these agents has been found to exert an impact upon chemotherapy-induced oral mucositis [27]. Finally, patients randomised to receive topical GM-CSF were found to be significantly younger than in the AA group. It is worth mentioning in this context that patients in the age group of 1–20 years have been shown to develop oral problems following chemotherapy more frequently (90%) than patients of 60 years of age or older (18%), even in the case of identical malignancies and/or identical regimens of cytotoxic chemotherapy [5]. An explanation for this finding could be the fact that cell renewal is decreased in older patients and the number of mitoses in the basal epithelium is higher in younger than in older patients [28]. Although the present trial did not include patients of a very young age, the said discrepancy is nevertheless unlikely to have influenced the results.

A difference in dose intensity of cytotoxic agents in general and of 5-FU in particular between the two treatment arms can be excluded as a reason for the above findings as cytotoxic drugs and dosages were comparable. This aspect deserves particular attention due to the fact that the efficacy of systemically administered colony-stimulating factors in the clinical management of chemotherapy-induced mucositis has been often correlated with neutropenia [9,17] and the disappearance of mucositis-associated symptoms with the return to regular neutrophil counts [9,10,17]. Yet, in the present study leucocytes and granulocytes were analysed before and after treatment and were neither decreased at the onset of oral mucositis nor increased following the topical administration of GM-CSF. Thus, a mere haematologically-mediated effect upon the course of oral mucositis can be excluded as an explanation for our findings, further corroborating the assumption that the development and course of oral mucositis represent a complex biological event characterised by sequential changes in epithelium and connective tissue in the present scenario, possibly modulated by GM-CSF [12,13,29].

A crucial factor for the development of oral mucositis lies in poor oral hygiene. Increased risk factors for the development for oral mucositis consist of generally poor oral health, pre-existing periodontal or pulpal disease [30], irritating prostheses or sharp and broken teeth. Although oral hygiene tended to be better in patients from the GM-CSF group as compared with the AA group, this discrepancy was probably neutralised by other similarities between study groups, including general tooth status, time elapsed since the last professional cleaning of teeth as well as the last dental visit.

Based upon the present findings, we conclude that topical application of GM-CSF might represent treatment-of-choice for oral mucositis induced by standard cytotoxic chemotherapy. An abbreviation of symptoms of oral mucositis which might influence mental health, contributes not only to an increase in patients' quality of life, but also to a reduction of costs [31] caused by the necessity of the patients' admission to the hospital for supportive care. If our findings could be reproduced by a new trial in a more homogeneously-selected patient population, treatment with topical GM-CSF might become established as standard treatment in oral mucositis.

References

1. Loprinzi CL, Dose AM. Studies on the prevention of 5-fluorouracil-induced oral mucositis. *NCI Monogr* 1990, **9**, 93–94.
2. Miaskowski C. Management of mucositis during therapy. *NCI Monogr* 1990, **9**, 95–98.
3. Sonis ST. Oral complications of cancer therapy. In DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology, 4th edn, 2387–2394JB. Philadelphia, Lippincott.
4. De Conno F, Ripamonti C, Sbanotto A, Ventafridda V. Oral complications in patients with advanced cancer. *J Palliat Care* 1989, **5**(1), 7–15.
5. Sonis ST, Sonis AL, Lieberman A. Oral complications in patients receiving treatment for malignancies other than the head and neck. *J Am Dent Assoc* 1978, **97**, 472–486.

6. Hejna M, Brodowicz T, Zielinski CC. Local use of GM-CSF for severe mucositis. *Eur J Cancer* 1999, **35**(3), 14–17.
7. Bodey GP. Fungal infections complicating acute leukemia. *J Chronic Dis* 1966, **19**, 667–687.
8. Pizzuto J, Conte G, Aviles A, *et al*. Nystatin prophylaxis in leukemia and lymphoma. *N Engl J Med* 1978, **299**, 661–662.
9. Gordon B, Spadinger A, Hodges E, *et al*. Effect of granulocyte-macrophage colony stimulating factor on oral mucositis after haematopoetic stem-cell transplantation. *J Clin Oncol* 1994, **12**, 1917–1922.
10. Chi KH, Chen CH, Chan WK, *et al*. Effect of granulocyte-macrophage colony stimulating factor on oral mucositis in head and neck cancer patients after cisplatin, fluorouracil, and leucovorin. *J Clin Oncol* 1995, **13**, 2620–2628.
11. Bonilla MA, Gillo AP, Ruggerio M, *et al*. Effects of recombinant human granulocyte-macrophage colony stimulating factor on neutropenia in patients with congenital agranulocytosis. *N Engl J Med* 1989, **320**, 1574–1580.
12. Bussolino F, Wang JM, Defilippi P, *et al*. Granulocyte colony-stimulating factor and granulocyte-macrophage stimulating-factor induce human endothelial cells to migrate and proliferate. *Nature* 1989, **337**, 471–473.
13. Jyung RW, Wu L, Pierce GF, *et al*. Granulocyte-macrophage colony stimulating factor ad of granulocyte colony stimulating factor granulocyte-macrophage colony stimulating factor: differential action on incisional wound healing. *Surgery* 1994, **115**, 325–334.
14. Raderer M, Kornek G, Hejna M, Koperna K, Scheithauer W, Base W. Topical granulocyte-macrophage colony-stimulating factor in patients with cancer and impaired wound healing. *J Natl Cancer Inst* 1997, **89**(3), 263.
15. Kaplan G, Walsh G, Guido LS, *et al*. Novel responses of human skin to intradermal recombinant granulocyte-macrophage colony stimulating factor: Langhans cell recruitment, keratinocyte growth, and enhanced wound healing. *J Exp Med* 1992, **175**, 1717–1728.
16. Boente P, Sampaio C, Brandao MA, Moreira ED, Badaro R, Jones TC. Local peri-lesional therapy with rhGM-CSF for Kaposi's sarcoma. *Lancet* 1993, **341**, 1154.
17. Grabrilove JL, Jakubowski A, Scher H, *et al*. Effect of granulocyte colony stimulating factor on neutropenia and associated morbidity of chemotherapy for transitional cell carcinoma of the urothelium. *N Engl J Med* 1988, **318**, 1414–1422.
18. Ovilla-Martinez R, Rubio ME, Borbolla JR, *et al*. GM-CSF mouthwashes as treatment for mucositis in BMT patients. *Blood* 1994, **84**(10) (abstr 2853).
19. Ibrahim EM, Al Mulhim FA. Effect of granulocyte-macrophage colony-stimulating factor on chemotherapy-induced oral mucositis in non-neutropenic cancer patients. *Med Oncol* 1997, **14**, 47–51.
20. Rovirosa A, Ferre J, Biete A. Granulocyte macrophage-colony-stimulating factor mouthwashes heal oral ulcers during head ad neck radiotherapy. *Int J Radiat Oncol Biol Phys* 1998, **41**(4), 747–754.
21. Karthaus M, Rosenthal C, Huebner G, *et al*. Effect of topical oral G-CSF on oral mucositis: a randomized placebo-controlled trail. *Bone Marrow Transplant* 1998, **22**(8), 781–785.
22. Sonis ST, Costello KA. A database for mucositis induced by cancer chemotherapy. *Eur J Cancer Oral Oncol* 1995, **31b**, 258–260.
23. Lembersky BC, Posner MC. Gastrointestinal toxicities. In Kirkwood JM, Lotze MT, Yasko JM, eds. *Current Cancer Therapeutics*. Princeton, Academic Press, 1994, 254–255.
24. Weisdorf DJ, Bostrom B, Raether D, *et al*. Oropharyngeal mucositis complicating bone marrow transplantation: prognostic factors ad the effect of chlorhexidine mouth rinse. *Bone Marrow Transplant* 1989, **4**, 89–93.
25. Foote RL, Loprinzi CL, Frank AR, *et al*. Randomized trial of a chlorhexidine mouthwash for alleviation of radiation-induced mucositis. *J Clin Oncol* 1994, **12**, 2630–2636.
26. Adamietz IA, Rahn R, Boettcher HD, Schaefer V, Reimer K, Fleischer W. Prophylaxis with povidone-iodine against induction of oral mucositis by radiochemotherapy. *Support Care Cancer* 1998, **6**, 373–377.
27. Dodd MJ, Miaskowski C, Shiba GH, *et al*. Risk factors for chemotherapy-induced oral mucositis: dental appliances, oral hygiene, previous oral lesions, and history of smoking. *Cancer Invest* 1999, **17**(4), 278–284.
28. Baraket NJ, Toto PD, Choukas NC. Aging and cell renewal of oral epithelium. *J Peridontal* 1969, **40**, 599–602.
29. Chi KH, Chan WK, Chen KY. Role of granulocyte-macrophage colony stimulating factor in chemoradiotherapy-induced oral mucositis. *J Clin Oncol* 1996, **14**(5), 1741–1743.
30. Greenberg MS, Cohen SG, McKifrick JC, *et al*. The oral flora as a source of septicemia in patients with acute leukemia. *Oral Surg* 1982, **53**, 28–32.
31. Ruescher TJ, Sodeifi A, Scrivani SJ, Kaban LB, Sonis ST. The impact of mucositis on alpha-hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. *Cancer* 1998, **82**(11), 2275–2281.