Original article

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Prophylaxis with GM-CSF mouthwashes does not reduce frequency and duration of severe oral mucositis in patients with solid tumors undergoing high-dose chemotherapy with autologous peripheral blood stem cell transplantation rescue: a double blind, randomized, placebo-controlled study

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Background: The aim of this study was to evaluate the effectiveness of granulocyte–macrophage colony-stimulating factor (GM-CSF) mouthwashes in the prevention of severe mucositis induced by high doses of chemotherapy.

Patients and methods: Ninety consecutive patients affected by solid tumors and undergoing high-dose chemotherapy with autologous peripheral blood stem cell transplantation rescue were randomized to receive placebo versus GM-CSF mouthwash 150 μg/day. Patients were stratified on the basis of the conditioning treatment and the consequent different risk of severe oral mucositis. Treatment was administered from the day after the end of chemotherapy until the resolution of stomatitis and/or neutrophil recovery.

Results: The statistical analyses were intention-to-treat and involved all patients who entered the study. The severity of stomatitis was evaluated daily by the physicians according to National Cancer Institute Common Toxicity Criteria. Both study and control groups were compared with respect to the frequency [30% versus 36%, χ^2 exact test, not significant (NS)] and mean duration (4.8 ± 4.7 versus 4.4 ± 2.7 days, *t*-test, NS) of severe stomatitis (grade ≥3). Oral pain was evaluated daily by patients themselves by means of a 10 cm analog visual scale: the mean (± standard error of the mean) maximum mucositis scores were 4.8 ± 3.5 versus 4.2 ± 3.5 cm (*t*-test, NS). Furthermore, 15/46 patients in the study group (33%) and 19/44 patients in the control group experienced pain requiring opioids (χ^2 exact test, NS).

Conclusion: We did not find any evidence to indicate that prophylaxis with GM-CSF mouthwash can help to reduce the severity of mucositis in the setting of the patients we studied.

Key words: GM-CSF, mouthwash, mucositis, prophylaxis

Introduction

The development of peripheral blood progenitor hematopoietic reconstitution significantly ameliorated the neutropenia associated with myeloablative therapy and revealed epithelial toxicity, such as mucositis, as the principal factor that limited further dose escalation. Various studies have demonstrated that significant stomatitis occurs in ~75% of patients undergoing stem cell transplantation [1, 2]. Severity varies widely between chemotherapy agents; high-dose etoposide and melphalan appear to cause the most serious forms of mucositis [2, 3]. Oral mucositis represents an important clinical problem because of the opiate-requiring pain, the need for parenteral nutrition, and the risk of mucosal infection and subsequent septicemia. Between 25% and 75% of bacteremias seen post-transplant may have disrupted oral mucous membranes as the portal of infection [3, 4]. Furthermore, in many patients undergoing myeloablative chemotherapy, the persistence of oral mucositis may delay the patient's discharge beyond hematological recovery. Granulocyte–macrophage colony-stimulating factor (GM-CSF) has a proven *in vitro* and *in vivo* activity on the proliferation of keratinocytes [5, 6], and data from animal models suggest that it enhances wound contraction and healing [7, 8]. Moreover, an experimental study in rats demonstrated that only local application of GM-CSF, in contrast to subcutaneous administration of GM-CSF or G-CSF, accelerates wound healing [8]. Data from humans are scant. Systemic administration of myeloid growth factors were reported to reduce the incidence of mucositis when given after standard dose chemo-

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therapy [9, 10], but the efficacy of mouthwashes is currently under investigation, and the results of several phase II trials and one small randomized clinical trial appear to be promising [11].

On the basis of such considerations, we designed a randomized, placebo-controlled clinical study to evaluate the efficacy of prophylaxis with GM-CSF mouthwash in reducing the incidence and severity of oral mucositis in patients undergoing high-dose chemotherapy and peripheral blood stem cell transplantation (PSCT) rescue for solid tumors.

Patients and methods

Patients fulfilling the enrollment criteria (age >14 years, hospitalized for high-dose chemotherapy with autologous PSCT rescue, provision of an informed consent) were randomly allocated to the GM-CSF or the placebo group. Patient characteristics are listed in Table 1. Conditioning regimens were categorized in two groups, high risk and low risk, based on the probability that they would induce mucositis (Table 1). Consequently, patients were prospectively stratified in two groups, according to the probability of experiencing mucositis. Study suspensions were prepared by the pharmacy unit and provided to the bone marrow transplant patients. Patients were supplied, in a double blind manner, with mouthwashes of GM-CSF 150 μg/day in 100 cm^3 of sterile water or 100 cm^3 of sterile water alone (placebo) in four doses per day. Patients were instructed to perform a 1 min mouthrinse each time. The color, odor, texture and taste of both solutions were virtually identical. All patients received conventional prophylaxis with 0.2% oral chlorhexidine and amphotericin B. Treatment was initiated on the day after the end of chemotherapy and continued either until bone marrow recovery (absolute neutrophil count >500/mm^3) or the resolution of mucositis (in case of persistent mucositis after bone marrow recovery). All patients received subcutaneous G-CSF 300 μg/day until hematopoietic reconstitution. Patients were examined daily by the physicians and results were prospectively recorded. The oral status was scored according to National Cancer Institute expanded common toxicity criteria (NCI-CTC) (Table 2) [12]. Mouth pain was self-evaluated daily by patients by means of a 10 cm analog visual scale. Opiate use was chosen as an objective measure of mucositis severity due to its quantitative nature and freedom from interobserver bias. All procedures followed were in accordance with the Helsinki Declaration of the World Medical Association.

Statistical analysis

Analyses were carried out on the intention-to-treat principle. It was estimated that 90 patients should be included to demonstrate a 25% minimal difference in the rate of severe mucositis (two-tailed test, $\alpha = 5\%$, $\beta = 10\%$). Differences between groups were evaluated by χ^2 test for categorical variables and Student's *t*-test for continuous variables. Mantel–Haenszel's χ^2 test was employed to analyze the two groups stratified on the basis of conditioning regimen.

Table 1. Patient characteristics

	GM-CSF ($n = 46$) (%)	Placebo ($n = 44$) (%)
Sex		
Male	27	24
Female	19	20
Age (years)		
Median	29	29
Range	15–57	17–61
Diagnosis		
Breast cancer	8 (17.5)	12 (27.5)
Ewing's sarcoma	19 (41.5)	13 (28.5)
Osteosarcoma	6 (13)	6 (14)
Non-Hodgkin's lymphoma	7 (15)	5 (11.5)
Germ cell tumors	5 (11)	7 (16)
Small-cell lung cancer	1 (2)	0
Soft tissue sarcoma	0	1 (2.5)
Conditioning regimen		
High risk[a]	26 (56.5)	26(59)
Low risk[b]	20 (43.5)	18 (41)

[a]High risk: ThioPAM: thiotepa 600 mg/m^2 and melphalan 140 mg/m^2; MitoxantroneThioCy: mitoxantrone 40 mg/m^2 day 1 + thiotepa 500 mg/m^2 day 2 + cyclophosphamide 100 mg/kg days 3–4; BusPAM: busulfan 4 mg/kg days 1–4 + melphalan 140 mg/m^2 day 5.
[b]Low risk: CarboPEC: carboplatine 550 mg/m^2, etoposide 450 mg/m^2 and cyclophosphamide 1600 mg/m^2 days 1–4; ICE: ifosphamide 3750 mg/m^2, carboplatine 450 mg/m^2 and etoposide 450 mg/m^2 days 1–4; BEAC: BCNU 300 mg/m^2 day 1 + etoposide 100 mg/m^2, cytarabine 100 mg/m^2 and cyclophosphamide 35 mg/kg days 2–5; BEAM: BCNU 60 mg/m^2 day 1 + melphalan 20 mg/m^2 day 2 + etoposide 200 mg/m^2 and cytarabine 100 mg/m^2 days 3–6; CE: carboplatine 375 mg/m^2 and etoposide 450 mg/m^2 days 1–4.

Table 2. Oral mucositis NCI-CTC criteria

Grade	Definition
0	No mucositis
1	Painless ulcers, erythema or mild soreness in the absence of lesions
2	Painful erythema, edema or ulcers, but can eat or swallow
3	Painful erythema, edema or ulcers requiring intravenous hydration
4	Severe ulceration or requires parenteral or enteral nutritional support

Results

Between July 1997 and February 2002 a total of 90 patients were randomized, 46 to the GM-CSF arm and 44 to the placebo arm. Baseline characteristics in the two groups were similar (Table 1), in particular in terms of type of conditioning regimens and consequently risk of mucositis. All but seven patients regularly completed mouthwashes: one patient in the control group did not perform any mouthrinse due to the persistence of vomiting, whereas the other six patients (four in the control group and two in the GM-CSF group) started their treatment but interrupted it early, also due to nausea and vomiting. The incidence of mucositis was similar in both groups (87% in the GM-CSF arm versus 95% in the placebo group, $P = 0.16$), as well as the occurrence of grade 3–4 stomatitis [33% versus 39%, χ^2 exact test, not significant (NS)]. We did not observe any statistically significant difference in terms of mean duration of stomatitis (4.8 ± 4.7 versus

4.4 ± 2.7 days, *t*-test, NS) between the two arms. Fifteen out of 46 patients in the study group (33%) and 19/44 patients in the control group (43%) experienced pain requiring narcotics (χ^2 exact test, NS). Eighty-seven per cent of patients in the GM-CSF group and 84% in the control group regularly put a mark on the visual analogic scale. Median days with oral pain were 9.7 and 8.4 respectively, and the mean (± standard error of the mean) maximum mucositis scores were 4.8 ± 3.5 versus 4.2 ± 3.5 cm (*t*-test, NS). The mean length of time with a mucositis score ≥4 cm was 3 days (± 3.35 days) in the GM-CSF group and 2.7 days (± 3.18 days) in the placebo group (*t*-test, NS). All results are listed in Table 3. The mean duration of absolute neutropenia was 7.5 days (± 2.8 days) in the study arm and 7 days (± 2.1 days) in the control group (*t*-test, NS). No differences in terms of further grade 3–4 toxicities were documented between the two groups (data not shown).

Table 3. Results

	GM-CSF (n = 46) (%)	Placebo (n = 44) (%)
Objective evaluation		
Incidence of stomatitis	40/46 (87)	42/44 (95)
High risk	25/26 (96)	25/26 (96)
Low risk	15/20 (75)	17/18 (94)
Severe stomatitis (grade 3–4)	15/46 (33)	17/44 (39)
High risk	9/26 (35)	9/26 (35)
Low risk	6/20 (30)	8/18 (44)
Duration of severe stomatitis (days)		
Mean	4.8 (± 4.7)	4.4 (± 2.7)
Median	4 (range 1–18)	5 (range 1–9)
Opiate use	15/46 (33)	19/44 (43)
Days with opiate		
Mean	2.7 (± 2)	3.8 (± 1.9)
Median	2 (range 1–6)	4 (range 1–6)
Other analgesics	12/46 (26)	13/44 (30)
Patient self evaluation		
Filling out diary	40/46 (87)	37/44 (84)
Absence of mouth pain	6/40 (15)	2/37 (5)
Time with mouth pain (days)		
Mean	9.7 (± 5.6)	8.4 (± 4.1)
Median	11 (range 0–20)	9 (range 0–17)
Maximum mucositis score (cm)		
Mean	4.8 (± 3.5)	4.2 (± 3.5)
Median	4.8 (range 0–10)	4.6 (range 0–10)
Time with pain ≥4 cm (days)		
Mean	3 (± 3.35)	2.7 (± 3.18)
Median	3 (range 0–12)	1.5 (range 0–10)

No difference is statistically significant.
Mean values ± standard error of the mean in parentheses.

Discussion

With the improved ability of managing other chemotherapy-related toxicities such as myelosuppression, oral mucositis is more and more frequently becoming the dose-limiting toxicity of intensive regimens. Currently, no intervention exists that is completely successful in preventing and treating chemotherapy-induced stomatitis. The observation of a beneficial effect of subcutaneous administration of CSF dates back to 1988, when Gabrilove et al. [9] demonstrated a decrease in the overall incidence of mucositis from 44% to 11% with patients receiving M-VAC (methotrexate 30 mg/m^2, vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2, cisplatin 70 mg/m^2) for transitional cell carcinoma of urothelium and randomized to receive G-CSF support. Other investigators have retrospectively observed that the duration and severity of oral mucositis can be decreased significantly by adding G-CSF or GM-CSF [13, 14]. The first prospective study to assess the potential efficacy of colony-stimulating factors on mucositis was reported by Chi et al. [10]. Twenty patients with metastatic squamous cell carcinoma of head and neck were randomized to receive cisplatinum, infusional fluorouracil and leucovorin with or without subcutaneous GM-CSF from day 5 to 14 of each cycle. The incidence of grade III mucositis, according to the Radiation Therapy Oncology Group criteria, was reduced from 73% to 11% with the addition of GM-CSF. In the transplant setting the benefits of myeloid growth factors have been less impressive however. Nemunaitis et al. [15] noted a reduction in mucositis in patients undergoing a human leukocyte antigen (HLA)-matched sibling allograft, whereas Atkinson et al. [16] did not show any difference in the incidence and severity of mucositis in patients receiving an HLA-matched sibling transplant with high-dose busulfan and cyclophosphamide. Preliminary data resulting from very small studies published in abstract form suggested that mouthwashing with GM-CSF might improve oral mucositis induced by chemotherapy [17, 18]. However, these expectations were not completely confirmed later. Cartee et al. [19] conducted a double-blind, placebo-controlled, dose-ranging study in patients with breast cancer during the first treatment cycle of a combination chemotherapy regimen, which has historically produced a 39% rate of grade 3–4 mucositis. Patients underwent prophylaxis with topical GM-CSF in a liquid mouthrinse. They did not observe a reduction in the maximum severity of mucositis between placebo and GM-CSF. Karthaus et al. [11] performed a prospective, randomized, placebo-controlled study using topical oral G-CSF in high-grade lymphoma patients to prevent chemotherapy-induced stomatitis. Eight patients were treated with 32 courses of chemotherapy. The administration of G-CSF mouthrinse significantly reduced the number of days in hospital, but the reduction in maximum severity of stomatitis was of borderline significance. A larger trial was carried out by van der Lelie et al. [20], who performed a double-blind, placebo-controlled study of 300 μg GM-CSF in a 2% methylcellulose gel daily versus a 2% methylcellulose gel alone in 36 consecutive patients undergoing stem cell transplantation. No differences were found in the median subjective pain scores, WHO scores, and oral assessment scores between the placebo and the GM-CSF groups.

All things considered, we have seen few randomized studies with too few patients so far. Our trial does not show any advantage for the group receiving GM-CSF mouthwashes in terms of the incidence, severity and duration of oral mucositis. It is well known that healing of mucositis is associated with neutrophil recovery. In our series the duration of absolute neutropenia was the same in both the treatment and control group. We administered subcutaneous G-CSF to all patients, and this could have mitigated the impact of topical GM-CSF. The sample size was calculated on a theoretical 90% incidence of grade 3–4 chemotherapy-induced stomatitis. In fact, the rate of severe oral mucositis was lower than expected (33%), which was probably due to the abandonment of autologous bone marrow transplantation with the definitive use of PSCT rescue, and to the unforeseeable new scenario of transplantation implying the progressive reduction of request for treatment of patients with advanced breast cancer, usually subjected to highly stomatotoxic treatments. Nevertheless stomatitis as a whole was documented in 82 out of 90 patients (91%) without any difference between the two groups.

To evaluate the severity of stomatitis we used the NCI-CTC. Interobserver variability remains the greatest problem in the routine use of this grading system, as well of the others, but the randomized, double-blind design of our study should have overcome this concern. Furthermore, the evaluation was completed by patient self-assessment. Every day each patient judged his oral pain and put a mark on a subjective visual analogic scale. We could not demonstrate any difference between the two groups either in terms of pain score or in terms of opiate consumption. All our patients underwent prophylactic daily mouthwashes with a 0.2% chlorhexidine solution. This has been tested as prophylaxis for mucositis in standard and high-dose chemotherapy and showed encouraging results in some studies [21, 22], but it failed to evidence benefit in larger series [23, 24]. Therefore, it seems unlikely that the use of chlorhexidine in our series would have contributed to lowering the incidence of stomatitis and hiding the possible beneficial effect of GM-CSF. We administered GM-CSF at a concentration of 1.5 μg/ml for a total daily dose of 150 μg. A previous study did not show any evidence of a dose–response relationship [19], even if a deleterious effect was achieved with a GM-CSF dose <0.1 μg/ml, and no differences were seen escalating GM-CSF concentration from 1 to 10 μg/ml.

In conclusion, our study is large enough, randomized and placebo controlled, and could contribute to the final answer on the utility of prophylaxis with GM-CSF mouthwashes in the setting of myeloablative chemotherapy, at least for patients scheduled to receive subcutaneous growth factors. We believe that future efforts should be concentrated in other directions. Some approaches seem promising, such as the employment of amifostine [25], oral pilocarpine [26], topical tretinoin [27] and oral glutamine [28]. Keratinocyte growth factor and interleukin-11 achieved interesting results in preclinical and phase I trials [29, 30]; however, since oral mucositis represents a major dose-limiting toxicity, large randomized trials are needed to better evaluate the activity of such promising agents.

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References

1. Woo SB, Sonis ST, Monopoli MM, Sonis A. A longitudinal study of oral ulcerative mucositis in bone marrow transplant recipients. Cancer 1993; 72: 1612–1617.
2. Pico JL, Avila-Garavito A, Naccachie P. Mucositis: its occurrence, consequences, and treatment in the oncology setting. Oncologist 1998; 3: 446–451.
3. Stiff P. Mucositis associated with stem cell transplantation: current status and innovative approaches to management. Bone Marrow Transplant 2001; 27 (Suppl 2): S3–S11.
4. Heimdahal A, Mattson T, Dahlof G et al. The oral cavity as a port for early infection in patients treated with bone marrow transplantation. Oral Surg Oral Med Oral Pathol 1989; 68: 711–716.
5. Davidson JM, Broadley KN. Manipulation of the wound healing process with fibroblast growth factor. Ann N Y Acad Sci 1991; 638: 307–315.
6. Rubbia L, Sappino AC, Gabbiani G. Locally applied GM-CSF induces the accumulation of alpha-smooth muscle actin containing myofibroblasts. Virchows Arch B Cell Pathol Incl Mol Pathol 1991; 60: 73–82.
7. Robson M, Kucukcelebi A, Carp SS et al. Effects of granulocyte–macrophage colony-stimulating on wound contraction. Eur J Clin Microbiol Infect Dis 1994; 3 (Suppl 2): S41–S46.
8. Jyung RW, Wu L, Pierce GF, Mustoe TA. Granulocyte macrophage colony-stimulating factor and granulocyte colony-stimulating factor: differential action on incisional wound healing. Surgery 1994; 115: 325–334.
9. Gabrilove JL, Jakubowski A, Scher H et al. Effect of granulocyte colony stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. N Engl J Med 1988; 318: 1414–1422.
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 chemotherapy. J Clin Oncol 1995; 13: 2620–2628.
11. Karthaus M, Rosenthal C, Huebner G et al. Effect of topical oral G-CSF on oral mucositis: a randomized placebo controlled trial. Bone Marrow Transplant 1998; 22: 781–785.
12. National Cancer Institute. Common Toxicity Criteria [online] (2003) http://ctep.cancer.gov/reporting/ctc.html.
13. Taylor KM, Jagannath S, Spitzer G et al. Recombinant human granulocyte colony-stimulating factor hastens granulocyte recovery after high-dose chemotherapy and autologous bone marrow transplantation in Hodgkin's disease. J Clin Oncol 1989; 7: 1791–1799.
14. Hermann F, Schulz G, Weiser M et al. Effect of granulocyte–macrophage colony stimulating factor on neutropenia and related morbidity induced by myelotoxic chemotherapy. Am J Med 1990; 88: 619–624.
15. Nemunaitis J, Rosenfeld CS, Ash R et al. Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. Bone Marrow Transplant 1995; 15: 949–954.
16. Atkinson K, Biggs JC, Downs K et al. GM-CSF after allogeneic bone marrow transplantation: accelerated recovery of neutrophils, monocytes and lymphocytes. Aust NZ J Med 1991; 21: 686–692.
17. Ovilla-Martinez R, Rubio ME, Borbolla JR et al. GM-CSF as treatment for mucositis in BMT patients. Blood 1994; 84: 10 (Abstr 2853).

18. Haus U, Quietzsch D, Faerber L et al. Effect of rh-granulocyte-macrophage colony-stimulating factor (GM-CSF) on oral mucositis. Ann Hematol 1996; 73 (Suppl 2): A51.
19. Cartee L, Petros WP, Rosner GL et al. Evaluation of GM-CSF mothwash for prevention of chemotherapy-induced mucositis: a randomized, double-blind, dose ranging study. Citokine 1995; 7: 471–477.
20. van der Lelie H, Thomas BLM, van Oers RHJ et al. Effect of locally applied GM-CSF on oral mucositis after stem cell transplantation: a prospective placebo-controlled double-blind study. Ann Hematol 2001; 80: 150–154.
21. Ferretti GA, Ash RC, Brown AT et al. Control of acute mucositis and candidiasis in marrow transplantation: a prospective double blind trial of chlorhexidine gluconate oral rinse. Bone Marrow Transplant 1988; 3: 483–493.
22. Ferretti GA, Hansen IA, Whittenburg K et al. Therapeutic use of chlorhexidine in bone marrow transplant patients: case studies. Oral Surg Oral Med Oral Pathol 1987; 63: 683–687.
23. Wahlin YB. Effects of chlorhexidine mouth rinse on oral health in patients with acute leukemia. Oral Surg Oral Med Oral Pathol 1989; 68: 279–287.
24. Weisdorf DJ, Bostrom B, Raether D et al. Oropharingeal mucositis complicating bone marrow transplantation: prognostic factor and the effect of chlorhexidine mouth rinse. Bone Marrow Transplant 1989; 4: 89–95.
25. Capelli D, Santini G, De Souza C et al. Amifostine can reduce mucosal damage after high dose melphalan conditioning for peripheral blood progenitor cell autotransplant: a retrospective study. Br J Haematol 2000; 110: 300–307.
26. Awidi A, Homsi U, Kakail RI et al. Double-blind, placebo-controlled cross over study of oral pilocarpine for the prevention of chemotherapy-induced oral mucositis in adult patients with cancer. Eur J Cancer 2001; 37: 2010–2014.
27. Cohen G, Elad S, Or R et al. The use of tretinoin as oral mucositis prophylaxis in bone marrow transplantation patients: a preliminary study. Oral Dis 1997; 3: 243–246.
28. Cockerham MB, Weinberger BB, Lerchie SB. Oral glutamine for the prevention of oral mucositis associated with high-dose paclitaxel and melphalan for autologous bone marrow transplantation. Ann Pharmacother 2000; 34: 300–303.
29. Zeeh JM, Procaccino F, Hoffmann P et al. Keratinocyte growth factor ameliorates mucosal injury in an experimental model of colitis in rats. Gastroenterology 1996; 110: 1077–1083.
30. Schwerkoske J, Schwartzberg L, Weaver CH et al. A phase I double-masked, placebo-controlled study to evaluate tolerability of Neumega® (rhIL-11; Oprelvelkin) to reduce mucositis in patients with solid tumors or lymphoma receiving high-dose chemotherapy (CT) with autologous peripheral blood stem cell reinfusion (PBSCT). Proc Am Soc Clin Oncol 1999; 18: 584a (Abstr 2256).