Effect of Granulocyte-Macrophage Colony-Stimulating Factor on Oral Mucositis in Head and Neck Cancer Patients After Cisplatin, Fluorouracil, and Leucovorin Chemotherapy

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Purpose: To evaluate prospectively the efficacy of granulocyte-macrophage colony-stimulating factor (GM-CSF) in the reduction of chemotherapy-induced oral mucositis.

Patients and Methods: Twenty patients with stage IV squamous cell carcinoma of head and neck were studied. Two-cycles (periods) of identical doses of cisplatin, fluorouracil (5-FU), and leucovorin (PFL) chemotherapy with cisplatin 20 mg/m^2/d, 5-FU 800 mg/m^2/d, leucovorin 90 mg/m^2/d by 96-hour continuous intravenous infusion every 3 weeks were given to each patient. After PFL chemotherapy, GM-CSF 4 μg/kg subcutaneously from days 5 to 14 or no therapy was given by a randomized self-controlled crossover study design. Oral mucositis was graded with modified Radiation Therapy Oncology Group criteria.

Results: In the first cycle of PFL chemotherapy, GM-CSF significantly reduced the incidence, mean duration, and mean area under the curve (AUC) of severe oral gross mucositis (grade ≥ 3) compared with no therapy. These beneficial effects continued into the second cycle of PFL chemotherapy after crossover to no GM-CSF. The incidence of severe mucositis was reduced when GM-CSF was given in the second cycle of PFL. Analysis of variance indicated significant direct GM-CSF treatment effects on the mean AUC of gross/functional scores and duration of moderate gross mucositis (grade ≥ 2) over both periods. There was a significant period effect in favor of giving GM-CSF in the first cycle of chemotherapy.

Conclusion: GM-CSF can significantly reduce the severity and duration of chemotherapy-induced oral mucositis after PFL chemotherapy.

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DESPITE HIGH response rates, oral musositis is one of the dose-limiting toxicities of cisplatin, fluorouracil (5-FU), and leucovorin (PFL) chemotherapy in squamous cell carcinoma of the head and neck region.[1-4] Oral mucositis (grade ≥ 2) was reported in up to 90% of cases after PFL chemotherapy.[4] Oral mucositis may be intensively painful and may lead to weight loss from odynodysphagia. The breakdown of the mucosal epithelium could be a potential portal for infection and a major risk of septicemia in chemotherapy-induced neutropenia. Oral mucositis after chemotherapy may be aggravated by neutropenia and local secondary infection.

The efficacy of recombinant human hematopoietic growth factors in improving the neutropenic state is well known.[5-9] A coincidental decrease in oral mucositis associated with granulocyte colony-stimulating factor (G-CSF) and methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) chemotherapy of genitourinary cancer was first reported by Gabrilove et al.[10] The mucosal protection effects of G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) were also observed in other chemotherapy regimens.[6,8,11-13] However, controversies existed in other clinical trials.[14,15] Most of these studies focused primarily on the myelocytic recovery effect of CSFs on intensive chemotherapy-induced myelotoxicities. One report showed a lowered incidence of oral mucositis when GM-CSF was given after 5-FU/leucovorin chemotherapy of low myelotoxicity.[16] It is uncertain whether GM-CSF has a direct salutary effect on the oral mucosal healing process independent of improvement of neutropenia.

No prospective randomized clinical trial has been conducted so far that has investigated the reduction of oral musoitis by GM-CSF as the primary study goal. The objective of this study was to evaluate prospectively the efficacy of GM-CSF on the reduction of severity and duration of PFL chemotherapy-induced musositis on head and neck cancer patients.

PATIENTS AND METHODS

Eligibility Criteria

Patients with diagnosis of stage IV squamous cell carcinoma of the head and neck region, previously untreated, or locally recurrent

Table 1. Oral Mucositis Grading Scores

Type of Score	Grade (symptoms)				
	0	1	2	3	4
Gross (assessed by physician)	None	Erythematous scores	Patchy mucositis (< 1/2 mucosa)	Confluent fibrinous mucositis (≥ 1/2 mucosa)	Hemorrhage and necrosis
Functional (assessed by patient)	None	Mild soreness, mild dysphagia, solid diet possible	Moderate pain, moderate dysphagia, soft diet or liquid diet possible	Severe pain, severe dysphagia, liquids only	Requires parenteral or enteral support

after previous surgery with/or radiotherapy, were eligible. An Eastern Cooperative Oncology Group performance status ≥ 2, adequate bone marrow function (leukocyte count ≥ 4,000/μL, platelet count ≥ 100,000/μL, and hemoglobin level ≥ 10.5 g/dL), liver function (bilirubin level ≤ 1.5 mg/dL), and renal function (serum creatinine concentration ≤ 1.5 mg/dL) were required. Patients could not have any concurrent medical illness, and no local radiotherapy to the oropharynx region within 3 months.

Treatment Plan

All patients received thorough oral examinations and preventive dental management before trial entry. Two cycles of identical doses of PFL chemotherapy were given to each patient. The PFL chemotherapy regimen consists of cisplatin 20 mg/m^2/d, 5-FU 800 mg/m^2/d, and leucovorin 90 mg/m^2/d for 96 hours by intravenous continuous infusion through an infusion pump and repeated at 3-week intervals.[4] Patients were randomized to receive GM-CSF or no therapy after the first cycle of PFL chemotherapy. A crossover study design was used for GM-CSF or no therapy after the second cycle of chemotherapy. The second cycle of chemotherapy could only be given when mucositis from the first cycle had been eliminated, and no dose modification of chemotherapy was allowed. GM-CSF (supplied by Schering Plough Corp, Kenilworth, NJ) was administered 4 μg/kg subcutaneously for 10 days from day 5 to day 14 after PFL chemotherapy. This study was approved by the institution's clinical review board. Written, informed consent was obtained from each patient.

Evaluation Methods

Patient's oral conditions were checked daily for 17 days by the physician after each cycle of chemotherapy. Oral mucositis were graded according to modified Radiation Therapy Oncology Group criteria. Gross and functional mucositis scoring criteria are listed in Table 1. Subjective pain and eating function were assessed by patients. Complete blood cell counts, and serum biochemistry profiles were performed before each cycle of chemotherapy and repeated weekly and every 3 weeks, respectively.

Statistical Methods

The sum of daily mucositis scores of each patient over 17 days after PFL chemotherapy with or without GM-CSF was used to approximate the area under the curve (AUC) of daily mucositis scores for individual subjects. The AUC and duration of gross mucositis (grade ≥ 2) were assessed using the analysis of variance model by the Grizzle-Hills-Armitage approach for a two-treatment, two-period, two-group trial.[17,18] The model in this study contains period (period 1 is defined as during chemotherapy cycle 1 and period 2

as during chemotherapy cycle 2), treatment, and carry-over effects. The outcome variables were the mean AUC of gross/functional mucositis scores and duration of gross mucositis (grade ≥ 2) over 17 days, respectively.

RESULTS

Twenty patients were entered onto the trial. Nine patients were randomized to receive GM-CSF and 11 patients to receive no therapy on the first cycle of PFL chemotherapy. Patients were crossed over at the second cycle of PFL chemotherapy. Patient characteristics are listed in Table 2. There were 18 men and two women. The median age was 45 years (range, 36 to 66). A total of 40 cycles of PFL chemotherapy were given over two treatment periods. Dose-intensity of PFL was identical in patients who received PFL chemotherapy alone or PFL chemotherapy plus GM-CSF. The tumor response rate (complete plus partial responses) in 17 patients with measurable disease was 82%.

Myelotoxicity was mild and two patients (10%) developed grade 3 neutropenia after PFL chemotherapy with or without GM-CSF. The median leukocyte nadirs were 5,300/μL and 5,200/μL in the PFL-alone arm and PFL-

Table 2. Patient Characteristics

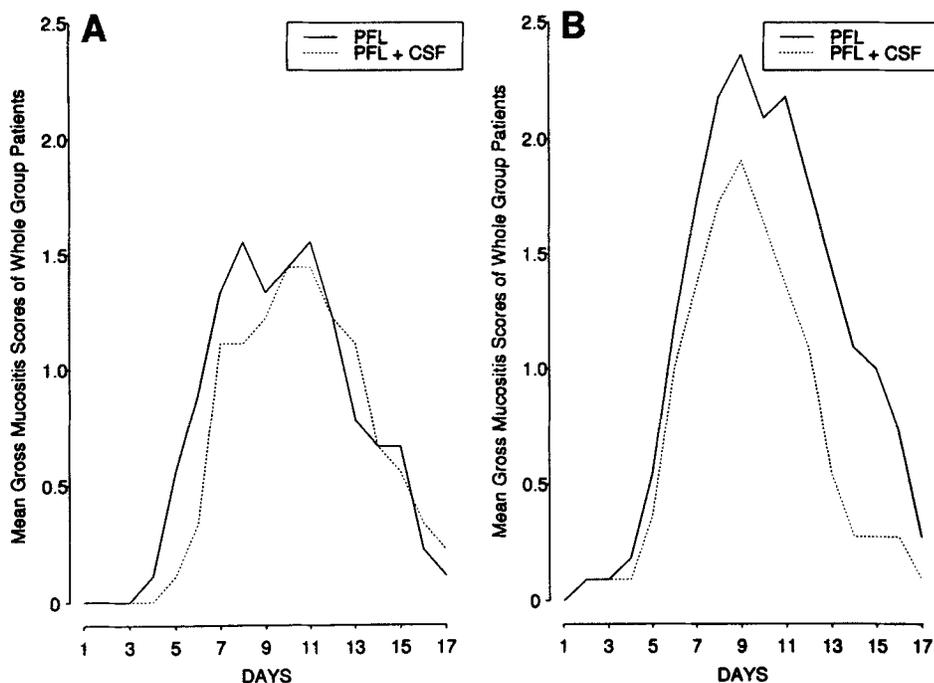| Characteristic	First Cycle With GM-CSF	Second Cycle With GM-CSF
Total no. of patients	9	11
Age, years		
Median	44	49
Range	36-62	40-66
Male/female (n)	8/1	10/1
Diagnosis (n)		
Nasopharyngeal cancer	4	3
Tongue cancer	2	4
Hypopharynx cancer	1	2
Buccal cancer	1	1
Tonsilar cancer	1	1
Prior therapy (n)		
Radiotherapy	3	3
Surgery	1	1
None	5	7

Fig 1. Mean daily gross mucositis scores over 17 days for patients who received PFL chemotherapy with or without GM-CSF in (A) the first cycle and (B) the second cycle.
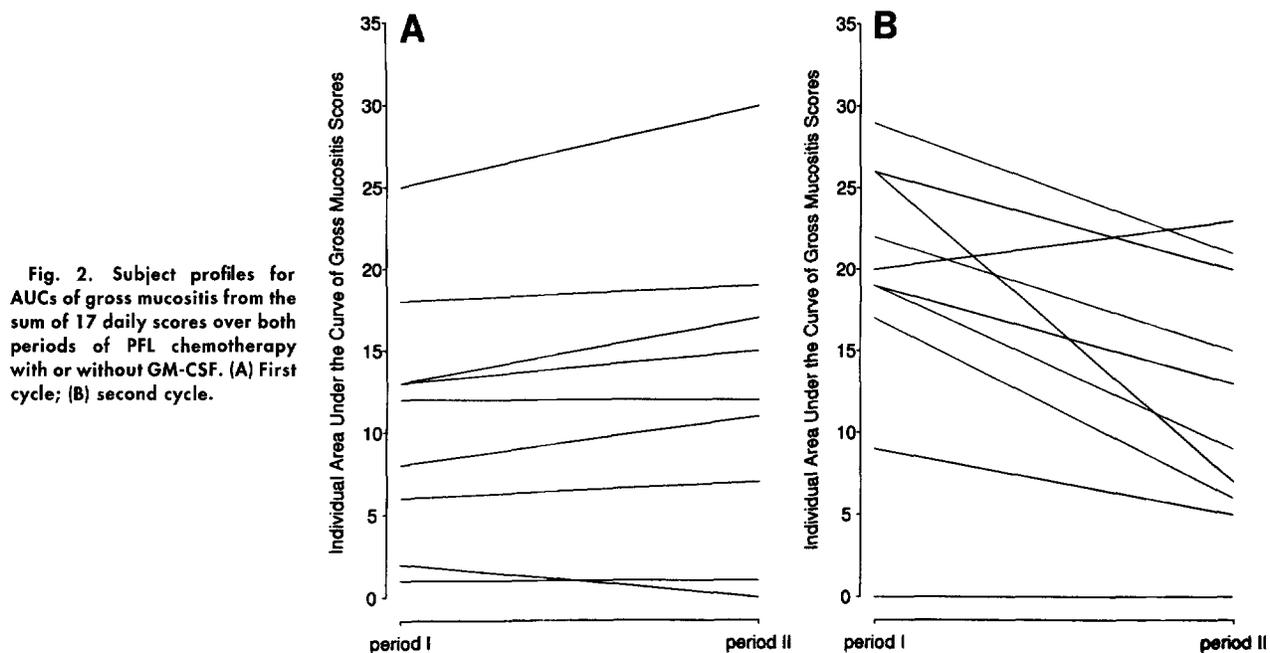
plus-GM-CSF arm, respectively. The median leukocyte count after GM-CSF treatment was 15,600 (range, 5,900 to 36,500). One patient had fever and chills, and two patients had general malaise and headache during GM-CSF treatment. No patient had evidence of fluid retention after GM-CSF.

There was significant reduction of gross mucositis by GM-CSF in the first cycle of PFL chemotherapy. The incidence of severe gross mucositis (grade ≥ 3) was reduced from 73% (eight of 11 patients) without GM-CSF to 11% (one of nine patients) with GM-CSF treatment. (P = .009, Fisher's exact test). The mean duration of severe gross mucositis were 0.3 days in patients with GM-CSF, compared with 2.5 days in those without GM-CSF (P = .006, two-sample t test). Concerning the effect of GM-CSF versus no therapy on the reduction of severe mucositis (grade ≥ 3) over both cycles of PFL chemotherapy, eight of 11 patients who did not receive GM-CSF in the first cycle of PFL chemotherapy had severe mucositis. However, four of these eight patients had reduction of mucositis after GM-CSF was given in the second cycle of PFL chemotherapy. Patients who received GM-CSF in the first cycle of chemotherapy appeared to have continued benefit of reduction of oral mucositis over both cycles.

The mean daily gross mucositis scores in the two groups of patients after cycles 1 and 2 of PFL chemother-

Table 3. Sum of Gross/Functional Daily Mucositis Scores and Duration of Gross Mucositis (grade ≥ 2) Assessed Over 17 Days

Cycle	Patient No.	Sum of Scores in 17 Days				Duration of Mucositis ≥ Grade 2 Gross (days)	
		Gross		Function			
		PFL	PFL + GM-CSF	PFL	PFL + GM-CSF	PFL	PFL + GM-CSF
Second cycle with GM-CSF	1	29	21	19	16	11	7
	2	0	0	0	0	0	0
	3	26	20	22	21	8	7
	4	22	15	18	12	6	4
	5	19	13	21	14	6	4
	6	19	9	20	11	6	2
	7	22	15	27	21	7	6
	8	9	5	14	11	0	0
	9	17	6	12	3	7	1
	10	20	23	22	22	7	7
	11	26	7	15	13	8	1
First cycle with GM-CSF	1	12	12	17	11	3	3
	2	30	25	33	22	11	9
	3	1	1	4	0	0	0
	4	19	18	23	18	7	7
	5	7	6	5	0	1	0
	6	15	13	14	13	5	3
	7	0	2	3	0	0	0
	8	17	13	22	16	5	5
	9	11	8	6	11	3	1

Fig. 2. Subject profiles for AUCs of gross mucositis from the sum of 17 daily scores over both periods of PFL chemotherapy with or without GM-CSF. (A) First cycle; (B) second cycle.

apy with or without GM-CSF are shown in Fig 1. The sums of individual patient's daily gross and functional mucositis scores over 17 days after PFL chemotherapy with or without GM-CSF are listed in Table 3. The sums of daily gross mucositis score of individual patients expressed as AUC plotted against corresponding periods is

shown in Fig 2. In the first cycle, the mean AUC values of gross mucositis were significantly reduced by GM-CSF. The mean AUC values of gross mucositis with or without GM-CSF were 10.9 and 19, respectively ($P = .037$ two-sample t test).

Figure 3 displays the groups-by-periods plot of mean
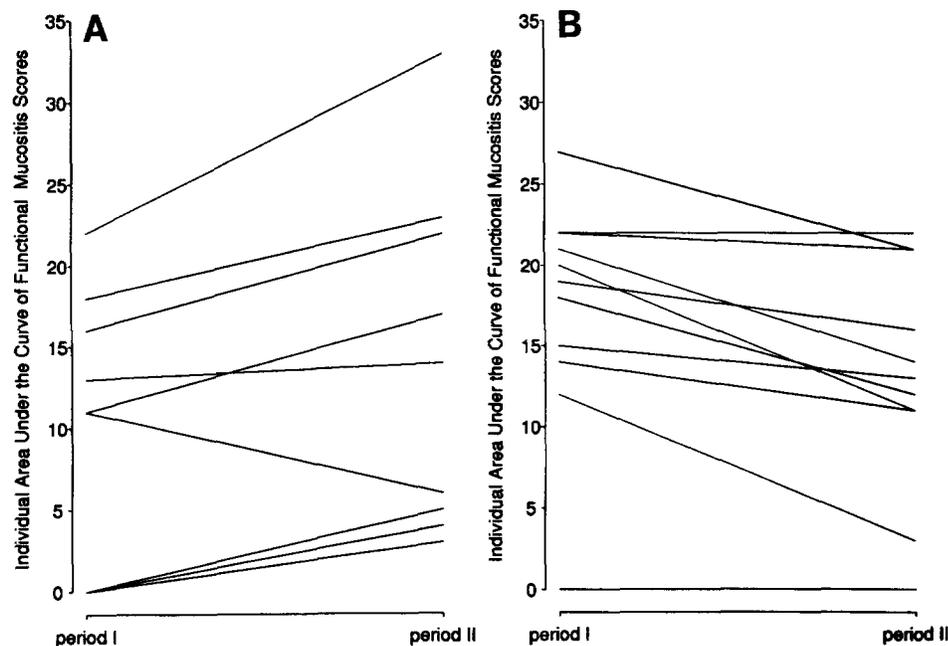
Fig 3. Subject profiles for AUC of functional mucositis from the sum of 17 daily scores over both periods of PFL chemotherapy with or without GM-CSF. (A) First cycle; (B) second cycle.
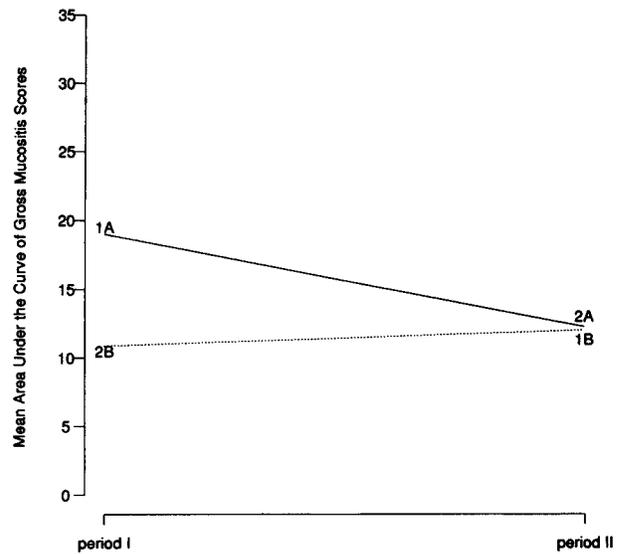
AUC of gross mucositis without (Fig 3A) or with (Fig 3B) GM-CSF between two periods of PFL treatment. Analysis of variance for the design of the two-treatment, two-period, two-group trial as listed in Table 4 indicates that there was not only a significant treatment effect of GM-CSF ($P < .001$), but also a significant period effect ($P < .01$). The carry-over effect was not statistically significant ($P = .14$). The 95% confidence interval for the reduction of mean AUC of gross mucositis due to direct GM-CSF treatment is 2.05 to 6.32. GM-CSF appeared to be significantly more effective in the reduction of mean AUC values of gross mucositis when given in the first cycle of PFL chemotherapy compared with the second cycle. The mean AUC values of treatment 2A (randomized to receive GM-CSF on cycle 1 and crossed over to no GM-CSF on cycle 2) were lowered almost to the level of treatment 1B (randomized to receive no therapy on cycle 1 and crossed over to receive GM-CSF on cycle 2). The subject profiles for AUC values of functional scores are plotted in Fig 4. Analysis of mean AUC values of functional scores also showed a significant treatment effect ($P < .001$). The 95% confidence interval for the reduction of mean AUC values of functional mucositis due to direct GM-CSF treatment is 2.28 to 5.90.

The duration of moderate gross mucositis (grade ≥ 2) for each subject over 17 days after PFL chemotherapy with or without GM-CSF is listed in Table 3, and the individual profiles are plotted in Fig 5. The result from the analysis of variance model indicates a significant direct GM-CSF treatment effect ($P < .001$) and period effect ($P = .036$), but no significant carry-over effect ($P = .19$). The groups-by-periods plot is given in Fig 6. The 95% confidence interval for the duration difference, due to direct GM-CSF treatment, of gross mucositis (grade ≥ 2) is 0.70 to 2.54 days.
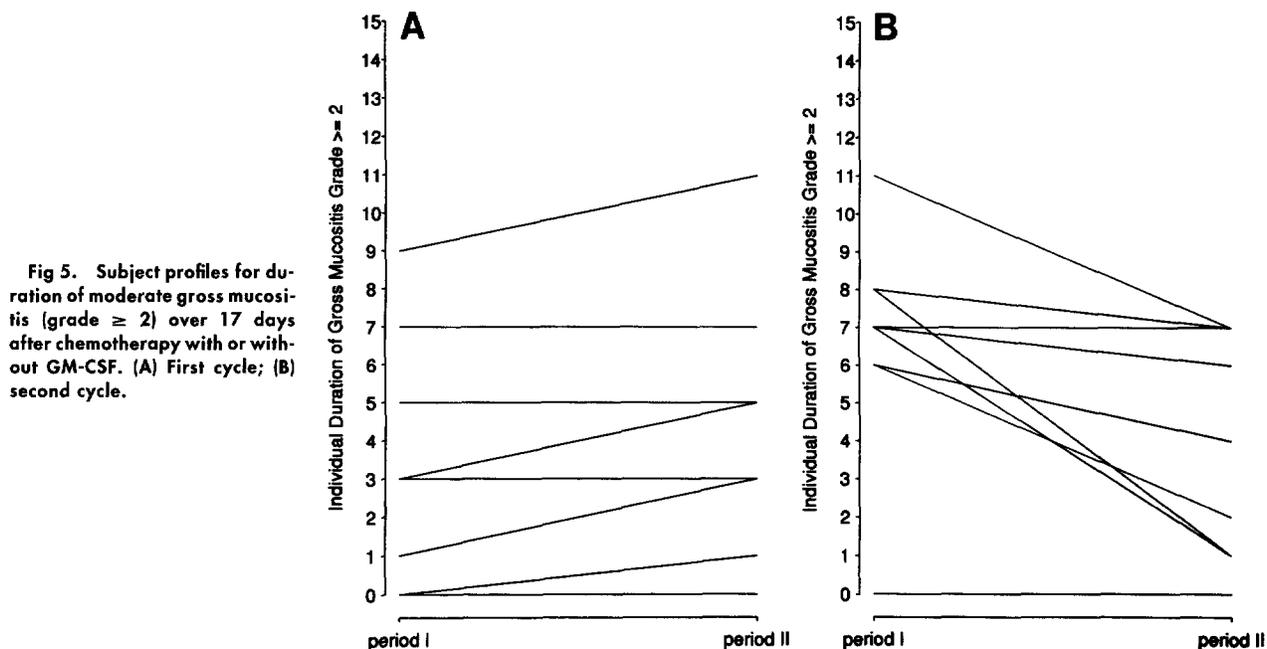

Fig 4. Groups-by-periods plot for mean AUC of gross mucositis from the 2-treatment, 2-period crossover design. Group 1, patients randomized to no therapy on the first cycle of PFL; group 2, patients randomized to GM-CSF treatment on the first cycle of PFL; (A) PFL alone; (B) PFL plus GM-CSF; (———) fixed PFL; (· · ·) fixed PFL plus GM-CSF.

DISCUSSION

Reduction of chemotherapy-induced oral mucositis was observed coincidentally with amelioration of neutropenia after chemotherapy in clinical trials of G-CSF or GM-CSF in cancer patients. Gabrilove et al[10] first reported a 75% decrease in the incidence of oral mucositis when G-CSF was included in the M-VAC chemotherapy regimen. A similar effect was observed when GM-CSF was given with doxorubicin, ifosfamide, and dacarbazine chemotherapy.[6] A decreased incidence of oral mucositis was also observed in bone marrow transplant patients given G-CSF or GM-CSF.[8,11-13] A beneficial effect of G-CSF on the incidence of oral mucositis in patients with small-cell lung cancer treated with cyclophosphamide, doxorubicin, and etoposide (CAE) chemotherapy was reported recently.[19,20] A reduction of the duration of oral mucositis by GM-CSF after high-dose chemotherapy and hematopoietic stem-cell transplantation was also observed recently.[21] However, most of these studies were investigating the effect of G-CSF or GM-CSF on neutropenia after intensive chemotherapy. Oral mucositis reduction was not the primary end point. Prospective, controlled clinical trials were not the method used to assess mucositis in the previous studies. The duration and severity of oral mucositis were often not assessed.

Table 4. Analysis of Variance for Comparison of the AUCs of Gross Mucositis Scores Over 17 Days

Variable	df	SS	F	P
Between subjects				
Carry-over effect	1	152.457	1.241	.14
Between-subject residuals	18	2210.818		
Within subjects				
Direct treatment effect (adjusted for period)	1	173.546	16.984	< .001
Period effect (adjusted for treatment)	1	68.546	6.708	< .01
Within-subject residuals	18	183.929		
Total	39	2813.775		

Abbreviation: SS, sum of squares.

Fig 5. Subject profiles for duration of moderate gross mucositis (grade ≥ 2) over 17 days after chemotherapy with or without GM-CSF. (A) First cycle; (B) second cycle.

This is the first randomized, prospective controlled clinical study to evaluate the effect of GM-CSF versus no treatment on the reduction of the severity and duration of chemotherapy-induced oral mucositis. A crossover design was used and every patient acted as his own control. PFL chemotherapy was selected for this study because it is effective in the treatment of head and neck cancers, but frequently induces oral mucositis. The dose of every cycle of PFL chemotherapy was held constant for all patients in this study so that the effect of GM-CSF on oral mucositis could interpreted be more clearly.

The results of this study indicated that GM-CSF is effective in the reduction of the severity and duration of chemotherapy-induced oral mucositis. The mechanism of reduction of chemotherapy-induced oral mucositis by GM-CSF is uncertain. One possibility is that chemotherapy-induced neutropenia may predispose the patient to oral infections, which may initiate or aggravate the severity or prolong the duration of oral mucositis. Patients with prolonged periods of neutropenia after chemotherapy were reported more likely to develop mucositis.[22] Oral ulcerations have also been reported in patients with congenital neutropenia.[23] A quantitative relationship between the degree of neutropenia and infection has been reported in cancer patients.[24] The critical neutrophil count appears to be 1,000/μL.[25] G-CSF or GM-CSF may be able to reduce chemotherapy-induced oral mucositis by shortening the duration of neutropenia after chemotherapy or by

benefiting the oral neutrophil level recovery.[26] However, the PFL chemotherapy given in this study was relatively nonmyelotoxic. All patients had neutrophil counts above the critical level of 1,000/μL. The incidence and severity of neutropenia were the same in patients with or without GM-CSF. Therefore, the reduction of oral mucositis by GM-CSF in this study does not appear to be related to the granulocyte stimulatory effect of GM-CSF.

Another mechanism of the beneficial effect of GM-CSF on chemotherapy-induced mucositis may be a direct stimulatory effect of GM-CSF on the growth or regeneration of the oral mucosa. Nonmyeloid tissue can respond to GM-CSF or express GM-CSF receptors.[27-29] GM-CSF may stimulate the oral mucosal cells to proliferate by enhancing interleukin-1 (IL-1) transcription and translation.[30] The protective effect of IL-1 on the lip mucosa against radiation and/or cytotoxic damage by increasing the proliferative rates of mucosal cells was reported by Zaghloul et al.[31] Oral mucosa may respond to stimulatory effects of GM-CSF, as suggested by the increase in oral mucositis and more myelotoxicity when chemotherapy and G-CSF were given concurrently.[32] Grem et al[16] also reported that myelotoxicity and mucositis were significantly increased when GM-CSF were given on day 1 as compared with day 6 of 5-day 5-FU/leucovorin chemotherapy. The incidence of myelotoxicity (grade ≥ 3) was 21% and of mucositis (grade ≥ 2) 42% at the dose level of 425 mg/m^2 5-FU when GM-CSF was given on day 1,
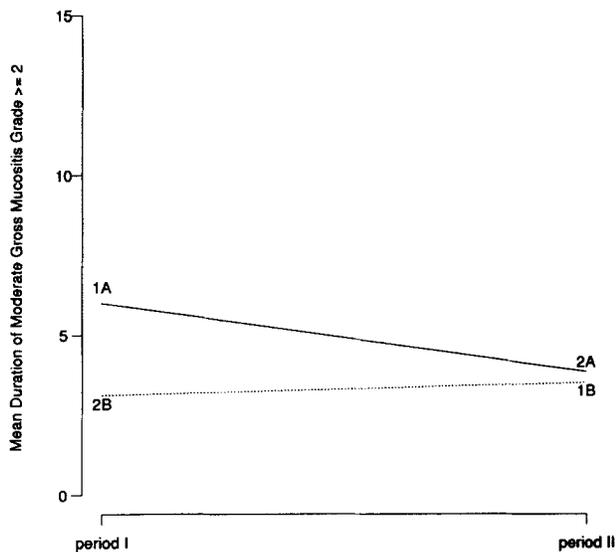
Fig 6. Groups-by-periods plot for mean duration of moderate mucositis (grade ≥ 2) from the 2-treatment, 2-period crossover design. Group 1, patients randomized to no therapy on the first cycle of PFL; group 2, patients randomized to GM-CSF on the first cycle of PFL; (A) PFL alone; (B,) PFL plus GM-CSF; (——) fixed PFL; (· · ·) fixed PFL plus GM-CSF.

while those values were 3.4% and 27% when GM-CSF was given on day 6. The explanation for the increase in myelotoxicity when G-CSF and GM-CSF are given concurrently with chemotherapy is thought to be stimulation of bone marrow progenitor cells and the increased pool of precusors susceptible to chemotherapy. The increase in mucositis after concurrent GM-CSF and chemotherapy suggests the stimulation of proliferative activity of oral mucosa by GM-CSF.

Evidence of changing mucositis status by modifying the oral mucosa proliferative rate before or during chemotherapy has been reported.[33,34] The administration of a mitogen, epidermoid growth factor, to the buccal cavity before chemotherapy exacerbates oral mucositis.[33] Transient arrest of cycling epithelial cells during chemotherapy may reduce the cytotoxic effects on oral mucosa. Topical application of tumor growth factor-β_3, a growth inhibitor of epithelial cells, transiently decreased oral epithelial proliferation and significantly reduced the severity and duration of oral mucositis from chemotherapy in a Syrian hamster model.[34] Oral cryotherapy with an ice cube to reduce blood flow in the oral mucosa and then to reduce the cell-drug exposure time may reduce the incidence of oral mucositis from 5-FU chemotherapy.[35] However, it may not be useful for patients treated by continuous chemotherapy (5-FU) infusion for several days.

GM-CSF given in the first cycle of PFL treatment may result in continued benefit in the second cycle of chemotherapy even when no GM-CSF was given. This can be misinterpreted as a prolonged carry-over effect. However, analysis of variance rejected the possibility of a carry-over effect. This may be statistically explained as a period effect in the crossover study. The mechanism of this phenoma is uncertain. One possibility may be the accelerated repopulation of preconditioned oral mucosa cells by the first cycle of chemotherapy. Accelerated clonogenic cell repopulation after radiotherapy and chemotherapy is recognized to be an important determinant of local tumor control and normal tissue tolerance, including tongue epithelium.[36-38] That is why oral mucositis is milder after an initial peak of mucositis during 5 to 7 weeks of irradiation.[39] The severity of oral mucositis is also milder during the second part of split-course radiotherapy than in the first part with the same total radiation dose for both parts.[39] Maciejewski et al[39] reported the effectiveness of reduction of mucositis by preconditioning by buring of oral mucosa by 2% silver nitrate solution a few days before radiotherapy. They suggested that silver nitrate can stimulate the unirradiated mucosa into a more effective proliferative state before the start of radiotherapy. Thus, the second cycle of PFL chemotherapy may be better tolerated by the preconditioned mucosa, analogous to mucositis reduction during the second part of split-course radiotherapy. We therefore hypothesize that the damage of oral mucosa after the first cycle of PFL chemotherapy may accelerate the ability of oral mucosa to regenerate and give an advantage to oral mucosa to face the next chemotherapy challenge. This observation may have major implications for the clinical management of chemotherapy-induced mucositis if this is confirmed by further clinical investigations.

In conclusion, GM-CSF can significantly reduce the severity and duration of chemotherapy-induced oral mucositis and improve the pain and eating function of patients after PFL chemotherapy. GM-CSF given after first cycle of chemotherapy may maintain the benefit on the oral mucosa even in the second cycle of chemotherapy. The role of GM-CSF in the reduction of chemotherapy-induced oral mucositis warrants further clinical investigation.

ACKNOWLEDGMENT

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