EFFECT OF GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR ON CHEMOTHERAPY-INDUCED ORAL MUCOSITIS IN NON-NEUTROPENIC CANCER PATIENTS

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الهدف من الدراسة: تهدف هذه الدراسة إلى تقييم كفاءة العامل المنشط لكرات الدم البيضاء في علاج التهابات الفم المصاحبة للعلاج الكيماوي لمرضى السرطان.
طريقة الدراسة: أجريت هذه الدراسة على 49 مريضا وتم استثناء 9 منهم لتناقص عدد كريات الدم البيضاء لديهم. الغالبية من الأربعين مريضا المتبقين (71%) كانوا يعانون من تقرحات بالفم من الدرجة الثالثة والرابعة.
نتائج الدراسة: أظهرت الدراسة أن العلاج أدى إلى تناقص علامات الإصابة الإجمالي ± معدل انحراف المتوسط من 3.3 ± 0.11 عند بداية التجربة إلى 2.1 ± 0.12 بعد يومين من العلاج وإلى 0.95 ± 0.11 بعد 5 أيام وإلى 0.23 ± 0.07 بعد 10 أيام، وكان التناقص ذو مغزى إحصائي. كما تناقص متوسط علامات الإصابة الوظائفية ± معدل انحراف المتوسط من 3.03 ± 0.13 عند بداية العلاج إلى 1.58 ± 0.13 بعد يومين من العلاج وإلى 0.68 ± 0.11 بعد 5 أيام ثم إلى 0.15 ± 0.06 بعد 10 أيام وهذا التناقص كان ذو مغزى إحصائي. وأثبتت الدراسة أن هناك قصر في مدة تقرحات الفم حيث كان 12 مريض (30%) لا يعانون من أي إصابة أو نقط من الدرجة الأولى في الإصابة الإجمالية بعد يومين من العلاج وتزايدت هذه النسبة إلى 37% بعد خمسة أيام ونسبة 100% عند انتهاء العلاج كما أن 19 مريضا (48%) وجدوا لا يعانون من أي إصابة أو نقط من الدرجة الأولى من الإصابة الوظائفية بعد يومين من العلاج وتزايدت هذه النسبة إلى 78% بعد خمسة أيام ونسبة 100% عند انتهاء العلاج كما أثبتت الدراسة عدم وجود أي آثار سلبية من العلاج.
الاستنتاجات: كان لاستخدام العامل المنشط لكرات الدم البيضاء في صورة مضمضة للفم تأثير واضح وأكيد على حدة ومدة تقرحات الفم الناتجة عن العلاج الكيميائي. ولهذا ننصح بإجراء دراسة كبيرة مقارنة مع البلاسيبو لتأكيد هذه الفائدة وتحديد الجرعة المثالية.
الكلمات المرجعية: العلاج الكيميائي، تقرحات الفم، العامل المنشط للخلايا البيضاء.

Objective: *The study was designed to assess prospectively the efficacy of granulocyte-macrophage colony-stimulating factor (GM-CSF) in the management of chemotherapy-induced oral mucositis in non-neutropenic cancer patients.*
Material and Methods: *In a prospective open study, adult cancer patients with chemotherapy-induced, neutropenia-independent oral mucositis were treated with GM-CSF (Schering Plough Corporation, Kenilworth, NJ) prepared as mouthwash solution (5 to 10 µgm /ml). GM-CSF was administered within 24 hours of occurrence of*
oral mucositis at a frequency of 4 to 6 times daily. Systemic GM-CSF was not permissible. Oral mucositis was graded according to the modified Radiation Therapy Oncology Group criteria.

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Results: *Forty-nine patients were recruited but nine were subsequently excluded as they experienced neutropenia during GM-CSF therapy. The remaining 40 patients were all evaluable. Most patients had either Grade 3 or 4 gross (71%) or functional (70%) mucositis. The mean ± SEM gross oral mucositis scores for all 40 patients combined decreased from 3.3 ± 0.11 at baseline to 2.1 ± 0.12 ($p<0.0001$) after 2 days, 0.95 ± 0.11 ($p<0.0001$) after 5 days and 0.23 ± 0.07 ($p<0.0001$) after 10 days of therapy. Likewise, the mean ± SEM functional oral mucositis scores decreased from 3.03 ± 0.13 at baseline to 1.58 ± 0.13 ($p<0.0001$) after 2 days, 0.68 ± 0.11 ($p<0.0001$) after 5 days, and 0.15 ± 0.06 ($p<0.0001$) after 10 days of therapy. The duration of severe oral mucositis was also shortened as Grade 0 or 1 (gross mucositis grading score) was evident in 12 (30%), 29 (73%), and 40 (100%) patients by the 2^{nd}, 5^{th} and 10^{th} day of therapy, respectively. Similarly, Grade 0 or 1 (functional mucositis grading score) reported in 19 (48%), 31 (78%), and 40 (100%) patients by the 2^{nd}, 5^{th} and 10^{th} day of therapy, respectively. The use of GM-CSF mouthwash was not associated with any apparent ill effect.*

Conclusion: *GM-CSF mouthwash as used in this study has a significant recuperative efficacy on the severity, morbidity, and duration of chemotherapy-induced oral mucositis. A large randomized, placebo-controlled study is warranted to ascertain that benefit and determine the optimal dosage and schedule.*

Key Words: *Chemotherapy, mucositis, G-CSF, GM-CSF*

INTRODUCTION

Oral mucositis as a consequence of cytotoxic therapy is a major cause of morbidity and dose-limiting toxicity in cancer patients. It was reported in up to 90% of patients after somatotoxic chemotherapy.[1] Moreover, the duration and severity of that complication is strikingly associated with high-dose chemoradiotherapy and hematopoietic stem-cell transplantation.[2-4] The pain in mucositis is usually intensively excruciating and may lead to weight loss from odynodysphagia. Furthermore, the breakdown of the mucosal epithelium barrier exposes cancer patients to infection and subsequent septicemia particularly in association with chemotherapy-induced neutropenia.[5,6] On the other hand, neutropenia and local secondary infection can also aggravate oral mucositis after chemotherapy. Moreover, severe sloughing of the oral mucosa may lead to airway compromise and may necessitate parenteral nutrition.

The efficacy of recombinant human hematopoietic growth factors in improving the neutropenic state is well documented.[7-11] Recently, a coincidental 75% 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.[12] The mucosal protection effects of G-CSF of granulocyte-macrophage colony-stimulating factor (GM-CSF) were also observed in other chemotherapy regimens.[13-16] One report showed a lowered incidence of oral mucositis when GM-CSF was given after 5-FU/leucovorin chemotherapy of low myelotoxicity.[17] In most of these reported studies, however, the effect

of hematopoietic growth factors on oral mucositis was not the primary end point.

Systemic administration of G-CSF or GM-CSF is effective in both reducing the severity and shortening the duration of neutropenia after chemotherapy. There is still some uncertainty as to whether GM-CSF has a direct salutary effect on the oral mucosal healing process independent of the improvement of neutropenia. However, a recently published crossover study has demonstrated the prophylactic efficacy of GM-CSF in head and neck cancer patients receiving a somatotoxic chemotherapy combination.[18] In this study, the reduction of the severity and duration of oral mucositis, that was the primary study goal, was independent of chemotherapy dose-intensity, myelotoxicity, or median leukocyte nadirs.

On the other hand, data that advocate the therapeutic efficacy of hematopoietic growth factors are very limited and only anecdotal.[19] We theorized that GM-CSF could have an advantageous therapeutic effect on oral mucositis that may be shown best if the agent is used as mouthwash. Our preliminary data on a small number of patients supported that concept.[20] Therefore, the present larger study was designed to assess the healing effect of GM-CSF mouthwash on oral mucositis independent of the confounding effect of neutropenia or its correction. The therapeutic strategy also eliminates the variability in somatotoxic potential of various chemotherapeutic agents.

PATIENTS AND METHODS

Eligibility criteria: In a prospective, open label study, adult patients seen at King Fahd Hospital of the University, Al-Khobar, with chemotherapy induced oral mucositis without neutropenia (neutrophilic count $\geq$ 2.0 x 10^9/l) were eligible. Patients were enrolled between July 1996 and June 1997. Patients who developed neutropenia during GM-CSF mouthwash were excluded from the main analysis. Patients could not have concurrent fungal or bacterial infection (as proven by culture), and no local radiotherapy to the oropharynx region within 3 months. Any agent that may ameliorate or worsen the mucositis was not permitted. Systemic GM-CSF was not routinely given, and rendered enrolled patients non-evaluable if required.

Treatment plan: GM-CSF(Schering Plough Corporation, Kenilworth, NJ) was prepared as a mouthwash solution with concentrations of 5 to 10 µgm/ml. The preparation was administered within 24 hours of occurrence of oral mucositis. Patients were instructed to use the solution 4 to 6 times daily and to retain and gargle the fluid for as long as possible. Therapy continued until complete resolution of the mucositis or if no benefit was achieved for 10 days. Informed written consent was obtained from each patient.

Evaluation methods: Patients were assessed daily and mucositis was graded according to modified Radiation Therapy Oncology Group criteria (Table 1).[18] The duration of mucositis was also determined. Complete blood cell counts were performed every other day or more frequent if indicated.

Statistical analysis: Mucositis scores are expressed as the mean ± SEM. The 't' test was used to compare the mean severity scores at entry for all patients combined against that at 2^{nd}, 5^{th}, and 10^{th} day of therapy. As multiple comparisons were used (6 for each type of mucositis score), based on the Bonferroni method, a conservative p value less than 0.008 was considered significant.

RESULTS

Forty-nine patients entered onto the trial. All patients had received somatotoxic chemotherapeutic agents mainly 5-flurouracil, methotrexate, and anthracylines. Nonetheless, neutropenia developed in 9 patients 4 of

whom experienced febrile episodes that required institution of systemic GM-CSF. All

Table 1: *Oral mucositis grading scores*

Type of Score	Grade (symptoms)				
	0	**1**	**2**	**3**	**4**
Gross (assessed by physician)	None	Erythema	Patchy mucositis (< ½ mucosa)	Confluent fibrinous mucositis (≥ ½ mucosa)	Hemorrhage and necrosis
Functional (assessed by patient)	None	Mild soreness, mild dysphagia, solid diet possible	Moderate soreness, moderate dysphagia, soft diet or liquid diet possible	Severe pain, severe dysphagia, liquids only	Requires parenteral or enteral support

9 patients were analyzed separately. The remaining 40 patients were evaluable and constituted the basis of this report. Table 2 depicts the clinical characteristics of those patients. There were 24 men and 16 women with a median age of 41 years (range, 18 to 75). Seventy-one percent and 70% of patients had either Grade 3 or 4 of the gross and functional mucositis grading scores, respectively.

Table 3 depicts the mean mucositis scores of all 40 patients combined at baseline and at the 2nd, 5th, and 10th day. The table shows that the mean mucositis scores, both gross and functional, decreased significantly as compared with estimates at entry.

The duration of severe oral mucositis was also shortened as Grade 0 or 1 (gross mucositis grading score) was evident in 12 (30%), 29 (73%), and 40 (100%) patients by the 2nd, 5th, and 10th day of therapy, respectively. Likewise, Grade 0 or 1 (functional mucositis grading score) reported in 19 (48%), 31 (78%), and 40 (100%) patients by the 2nd, 5th, and 10th day of therapy, respectively. The use of GM-CSF mouthwash was not associated with any apparent ill effect.

As for the 9 patients excluded from the analysis due to neutropenia, subjective and objective improvement was demonstrated within 3 to 4 days of therapy.

DISCUSSION

Reduction of chemotherapy-induced oral mucositis was first observed coincidentally with amelioration of neutropenia after chemotherapy in clinical trials of G-CSF or GM-CSF in cancer patients.[12] A decreased incidence of oral mucositis was also observed in bone marrow transplant patients given G-CSF

Table 2: *Patients' characteristics*

Characteristic	No. of patients (%)
Total no. of patients	40
Sex	
Males	24 (60)
Females	16 (40)
Diagnosis	
Breast	12 (30)
Head and neck	9 (23)
Lung	7 (18)
Non-Hodgkin's lymphoma	6 (15)
Colon	4 (10)
Hepatocellular carcinoma	1 (4)
Choriocarcinoma	1 (4)
Gross mucositis grading score at baseline	
1	2 (5)
2	10 (25)
3	15 (38)
4	13 (33)
Functional mucositis grading score at baseline	

1	2 (5)	4	8 (20)
2	10 (25)		
3	20 (50)		

Table 3: *Mean mucositis grading scores for all 40 patients combined at baseline and compared to that at the 2nd, 5th and 10th day*

	Gross Oral Mucositis Grading Scores (mean ± SEM)		
	Baseline (3.30 ± 0.11)	**2nd day (2.10 ± 0.12)**	**5th day (0.95 ± 0.11)**
2nd Day (2.10 ± 0.12)	P<0.0001		
5th Day (0.95 ± 0.11)	P<0.0001	P<0.0001	
10th Day (0.23 ± 0.07)	P<0.0001	P<0.0001	P<0.0001
	Functional Oral Mucositis Grading Scores (mean ± SEM)		
	Baseline (3.03 ± 0.13)	**2nd day (1.58 ± 0.13)**	**5th day (0.68 ± 0.11)**
2nd Day (1.58 ± 0.13)	P<0.0001		
5th Day (0.68 ± 0.11)	P<0.0001	P<0.0001	
10th Day (0.15 ± 0.06)	P<0.0001	P<0.0001	P<0.0001

or GM-CSF.[13-17] The results from the first randomized, prospective controlled clinical study to evaluate the effect of GM-CSF versus no treatment indicated that GM-CSF was effective in the reduction of the severity and duration of chemotherapy-induced oral mucositis.[18]

Preliminary data on a small number of patients supported the therapeutic efficacy of GM-CSF on oral mucositis.[20] The present larger study confirmed the earlier conclusion as it showed a significant expeditious lowering of the severity, morbidity, and duration of oral mucositis independent of an effect of granulocyte stimulatory effect of GM-CSF. The mean mucositis grading scores, both gross and functional, decreased significantly as compared with estimates at base level. Moreover, the duration of severe oral mucositis was also shortened as Grade 0 or 1 (gross mucositis grading score) was apparent in 30%, 73% and 100% of patients by the 2nd, 5th and 10th day of therapy, respectively. Similarly, Grade 0 or 1 (functional mucositis grading score) reported in 48%, 78%, and 100% of patients by the 2nd, 5th, and 10th day of therapy, respectively.

The mechanism of reduction of chemotherapy-induced oral mucositis by G-CSF or GM-CSF is uncertain. One plausible reason may be 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. Therefore, 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.[21] Nevertheless, the benefit shown in our study and that of Chi et al[18] was independent of systemic or local neutrophil recovery effect.

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. GM-CSF may stimulate the oral mucosal cells to proliferate by enhancing interleukin-1 transcription and translation.[22] The latter mechanism is connoted by the increase in oral mucositis and more myelotoxicity when chemotherapy and G-CSF were given concurrently.[17,23] The elucidation for the increase in myelotoxicity when G-CSF and GM-CSF are given concurrently with chemotherapy is attributed to the stimulation of bone marrow progenitor cells and the increased pool of precursors responsive to chemotherapy.[17] In another study, concurrent administration of GM-CSF mouthwash with

chemotherapy produced more oral mucositis as compared with placebo (42% vs 22%).[24]

In conclusion, therapeutic GM-CSF mouthwash can significantly reduce morbidity, severity, and duration of chemotherapy-induced oral mucositis. The effect is presumably related to its favorable acceleration of mucosal cells regeneration. The role of G-CSF or GM-CSF on chemotherapy-induced oral mucositis warrants a large, randomized, placebo-controlled clinical trial.

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