Surg Today
Jpn J Surg (1995) 25:202–206

SURGERY TODAY

Effect of Granulocyte Colony-Stimulating Factor (G-CSF) on Chemotherapy-Induced Oral Mucositis

MITSUO KATANO, MITSUNARI NAKAMURA, TATSUYA MATSUO, AKIHIRO IYAMA, and TAKEHARU HISATSUGU

Department of Surgery, Saga Medical School, 5-1-1 Nabeshima, Saga, 849 Japan

Abstract: In this study, the ability of granulocyte colony-stimulating factor (G-CSF) to treat or prevent chemotherapy-induced oral mucositis in patients with advanced breast cancer was evaluated. A total of 14 patients who received intra-arterial (i.a.) adriamycin (ADM) preoperatively were divided into two groups according to whether or not G-CSF was given. Thus, group A ($n = 7$) was given G-CSF and group B ($n = 7$) was not. G-CSF therapy reduced both the incidence and duration of ADM-induced oral mucositis, and a positive correlation was also seen between the incidence of mucositis and ADM-induced leukopenia (<2,000/mm^3). Group A was further divided into two subgroups according to whether G-CSF was given after or before the leukopenia had dropped below 2,000/mm^3: group A-1 ($n = 3$) and group A-2 ($n = 4$), respectively. ADM-induced mucositis was observed in two of the three patients in group A-1, but in none of the four patients in group A-2. These results strongly support the idea that G-CSF can effectively treat and prevent ADM-induced oral mucositis.

Key Words: oral mucositis, granulocyte colony-stimulating factor (G-CSF), adriamycin, chemotherapy

Introduction

Oral mucositis is one of the dose-limiting complications of such chemotherapeutic agents as adriamycin (ADM) and 5-fluorouracil (5-FU),[1–8] and patients with cyclic neutropenia have regularly recurring symptoms of fever and mucosal ulcers during periods of neutropenia.[9,10] The granulocyte colony-stimulating factor (G-CSF) is a neutrophil-specific growth factor,[11,12] which has been shown to increase the absolute neutrophil count in clinical trials conducted on patients with chemotherapy-induced leukopenia.[13,14] It has also been demonstrated that G-CSF therapy reduces the frequency of oropharyngeal inflammation in patients with cyclic neutropenia,[9,15,16] a finding supported by Gabrilove et al.[17] who reported that G-CSF reduced the incidence of chemotherapy-induced mucositis. These results indicate that G-CSF can reduce both the hematopoietic and oral toxicity of chemotherapy. In the present study, we evaluated whether the administration of G-CSF could treat or prevent chemotherapy-induced oral mucositis.

Reprint requests to: M. Katano
(Received for publication on Feb. 18, 1994; accepted on Nov. 10, 1994)

Materials and Methods

Patients and Treatment Procedure

A total of 14 patients with breast cancer (7 with primary advanced breast cancer, 5 with inflammatory breast cancer, and 2 with recurrent breast cancer) were treated preoperatively with intra-arterial (i.a.) high-dose adriamycin (ADM) 10 to 40 mg every 2–3 days, receiving a total dose of 70–170 mg. All the patients had normal neutrophil counts of 3,200–9,500/mm^3 when they were randomized into two groups of 7 patients each, prior to ADM therapy, according to whether G-CSF was to be given (group A) or not (group B). Both groups of patients had similar characteristics in all the factors examined, including age, leukocyte count before ADM therapy, cumulative dosages of ADM, and performance status (Table 1). The group A patients were further divided into two subgroups according to whether the daily subcutaneous (s.c.) injection of G-CSF 125 μg was given before (group A-1; $n = 4$) or after (group A-2; $n = 3$) the leukocyte counts were likely to drop below 2,000/mm^3. The administration of G-CSF was ceased when the leukocyte counts exceeded 8,000/mm^3.

Table 1. Clinical characteristics of the breast cancer patients in this study

Factors	Group A (n = 7)	Group B (n = 7)
Age (years)	38–69 (53.4 ± 10.5)	45–69 (51.6 ± 10.0)
Tumor stage[a]		
$T_2N_2M_0$	1	0
$T_2N_3M_0$	1	2
$T_2N_3M_1$	0	3
Inflammatory[b]	3	0
Recurrent[c]	1	1
Performance status:0	7	7
Total amount (ADM:mg)	128.6 ± 15.7	114.3 ± 20.7
Leukocyte count (/mm^3)		
before ADM therapy	5,313 ± 3,026	5,743 ± 1,243
G-CSF therapy	Received	Not received

[a] TNM classification (UICC, 1987)
[b] Inflammatory breast cancer
[c] Recurrent breast cancer

The patients who developed oral mucositis were treated only with conservative therapy using iodine solution for oral hygienic management.

Oral Examination

All patients underwent an oral examination 1 to 7 days before ADM therapy, then every day after the ADM therapy had been commenced. The oral examinations were performed at the bedside, and all the soft tissues were evaluated for erythema and ulceration. A definite diagnosis of mucositis was made according to the World Health Organization classification,[18] and all examinations were performed by a single experienced clinician. In this trial, patients were diagnosed as having mucositis if oral ulceration of at least grade 2 was present, while the tissue was judged to be normal if it was evaluated as grade 0 or 1.

G-CSF

Recombinant human G-CSF (Neutrogin) was provided by Chugai Pharmaceutical (Tokyo, Japan). Briefly, Neutrogin derived from Chinese hamster ovary cells,[19] which is structurally equivalent to natural human G-CSF,[20] was used.

Results

Neutrophil Response

Figure 1 shows the serial blood-leukocyte counts. A rapid decrease in the leukocyte count was induced in all the patients following the intra-arterial administration of ADM. All of the seven patients in group A responded to G-CSF with a rapid increase in their leukocyte counts, to a range of 8,200 to 17,000/mm^3 within 14 days after the completion of ADM therapy. On the other hand, the seven patients in group B showed a continuous decrease or a slow increase in their leukocyte counts, to a range of 1,200–3,800/mm^3 14 days after the completion of ADM therapy. Thus, treatment with G-CSF during or after ADM therapy not only induced a rapid increase in the leukocyte count but also reduced the duration of leukopenia (<2,000/mm^3). These results indicate that G-CSF can shorten the period of leukopenia or prevent its occurrence.

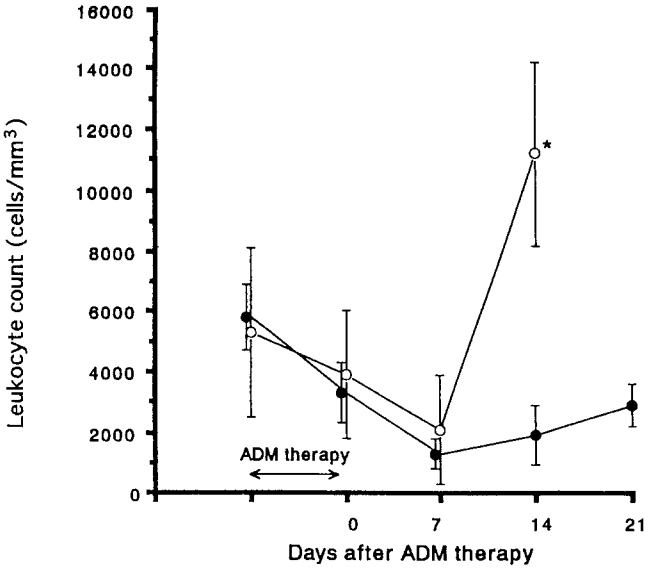

Fig. 1. Serial peripheral blood leukocyte counts. Group A (*open circles*): patients administered G-CSF after or during ADM therapy. Group B (*closed circles*): patients administered ADM therapy alone without G-CSF. *$P < 0.01$ (Student's t-test)

Oral Mucositis

All seven of the group B patients developed oral mucositis of grade 2 to 4,5–8 days after the commencement of ADM therapy, with a median onset of 6 days. The mean duration of mucositis was 13.7 days, with a range of 8–17 days. The patients had mucositis when the peripheral blood leukocyte counts were less than 2,000/mm^3 (Table 2). Episodes of fever occurred in five of these seven patients, one of whom developed adult respiratory distress syndrome (ARDS).

Mucositis developed in only two of the seven group A patients, occurring 7 days after the commencement of ADM therapy, the mean duration of which was 6.0 days (Table 2). Both these patients had been given G-CSF when the leukocyte count was less than 2,000/mm^3, being part of group A-1 (n = 3). However, none of the four patients in group A-2 who were given G-CSF before the leukocyte counts had dropped below 2,000/mm^3 had mucositis of grade 2 or worse (Table 3). Episodes of fever occurred in only one patient from group A-1.

These results indicate that G-CSF may reduce the incidence and duration of mucositis induced by ADM, although this effect may be partly induced by increasing the number of leukocytes, and therefore their functional ability to guard the mucosal barriers more efficiently.

Table 2. Incidence of oral mucositis

Symptoms	Group A (n = 7)	Group B (n = 7)
Mucositis		
Incidence	2*	7
Duration (days)	6.0 ± 0.0	13.7 ± 4.1
Alopecia	7	7
Fever (>38°C)	1*	5
ARDS	0	1

ARDS, adult respiratory distress syndrome
* $P < 0.05$ (χ^2-test)

Table 3. Preventive effect of G-CSF on ADM-induced mucositis

Factors and symptoms	Group A-1 (n = 3)	Group A-2 (n = 4)
Age (years)	38–56 (48.3)	48–69 (57.3)
Stage		
$T_2N_2M_0$	1	0
$T_2N_3M_0$	1	0
Inflammatory	1	3
Recurrent	0	1
Total amount (ADM:mg)	146.7 ± 25.2	125.0 ± 17.3
Leukocyte count (/mm^3)		
before ADM therapy	4,767 ± 1,779	6,800 ± 1,867
Leukocyte count (nadir)	967 ± 473	2,725 ± 2,343
Total amount (G-CSF:μg)	1,083 ± 191	1,031 ± 188
Mucositis	2	0
Alopecia	3	4
Fever (>38°C)	1	0

Discussion

In this report we documented the preliminary results of administering G-CSF therapy to patients with breast cancer complicated by ADM-induced neutropenia and oral mucositis. Our results demonstrate that G-CSF administered as an adjunct to intra-arterial ADM to patients with advanced breast cancer resulted in a significant reduction in the incidence, duration, and severity of oral mucositis. Chemotherapeutic agents induce dose-limiting toxicity not only in bone marrow cells but also in rapidly dividing epithelial cells of the mucosal surfaces. Oral mucositis is frequently induced when 5-FU is administered as a 5-day intensive course with concomitant leucovorin.[2] Mucositis evidently occurs when 5-FU is taken up by the dividing cells of the oral mucosa, which suggests that the mucositis may be induced by a direct toxicity of 5-FU. It has also been reported that the combination of doxorubicin, methotrexate, and vinblastine induces direct injury to oral and intestinal epithelium, and that this toxic injury occurs independently of the myelosuppressive toxic effects of these drugs.[21] It was recently demonstrated that an increase in the serum level of granulocyte-macrophage colony-stimulating factor (GM-CSF) corresponded to an improvement in the oral lesions of herpetic gingivostomatitis.[22] Although it was not ascertained whether the serum level of G-CSF as well as GM-CSF increased in our patients, this finding indicates that G-CSF may play a protective role against inflammation of the oral mucosal epithelium.

Mucositis and leukopenia, especially neutropenia, are also frequent complications of combination chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin.[23] Oral infections, especially by the herpes virus, are a frequent cause of oral ulceration in patients receiving intensive chemotherapy.[24] Furthermore, it is well known that primary neutropenic disorders including cyclic neutropenia,[9,10,15,16] Kostmann's syndrome,[25] and idiopathic neutropenia[26] are frequently complicated by oral ulcerations, which suggests that a significant decrease in the neutrophil count may induce oral mucositis. According to our experiments, mucositis occurred when the neutrophil count decreased to less than 2,000/mm^3, while ADM-induced mucositis became less severe as the neutrophil count increased. Thus, it is to be expected that reducing the period of neutropenia or preventing its occurrence can

reduce the incidence and duration of mucositis. G-CSF is a hematopoietic growth factor that promotes the proliferation and differentiation of neutrophils.[11–14] It also enhances the functional properties of mature cells by increasing phagocytic ability and antimicrobial killing.[27–30] In this study, G-CSF either significantly shortened the duration of chemotherapy-induced leukopenia or prevented its occurrence (Fig. 1) in accordance with reports by many investigators.[13,14,17] G-CSF also decreased both the incidence and duration of fever, indicating that G-CSF-induced neutrophils have the functional ability to protect the mucosal barriers (Tables 2 and 3).

In conclusion, the incidence of both oral mucositis and fever with leukopenia induced by the intra-arterial administration of ADM was significantly reduced in breast cancer patients treated with G-CSF during or after intensive chemotherapy. Moreover, administering G-CSF before the neutrophil count drops below 2,000/mm^3 may be the most effective for preventing ADM-induced mucositis. However, further investigations on the precise mechanisms of the effect of G-CSF on ADM-induced oral mucositis are still being conducted.

References

1. Samueles BL, Vogelzang NJ, Ruane M, Simon MA (1987) Continuous venous infusion of doxorubicin in advanced sarcomas. Cancer Treat Rep 71:971–972
2. Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, Krook JE, Mailliard JA, Laurie JA, Tschetter LK (1989) Biochemical modulation of fluorouracil: Evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7:1407–1418
3. Hederson JC, Allegra JC, Woodcock T, Wolff S, Bryan S, Cartwright K, Dukart G, Henry D (1989) Randomized clinical trial comparing mitoxantrone with doxorubicin in previously treated patients with metastatic breast cancer. J Clin Oncol 7:560–571
4. Gabizon A, Peretz T, Sulkes A, Amselem S, Ben-Yosef R, Ben-Baruch N, Catane R, Biran S, Berenholz Y (1989) Systemic administration of doxorubicin-containing liposomes in cancer patients: a phase I study. Eur J Cancer Clin Oncol 25: 1795–1803
5. Hortobagyi GN, Frye D, Buzdar AU, Ewer MS, Fraschini G, Hug V, Ames F, Montague E, Carrasco CH, Mackay B, Benjamin RS (1989) Decreased cardiac toxicity of doxorubicin administered by continuous intravenous infusion in combination chemotherapy for metastatic breast carcinoma. Cancer 63: 37–45
6. Mohood DJ, Dose AM, Loprinzi CL, Veeder MH, Athmann LM, Therneou TM, Sorensen JM, Gainey DK, Malliard JA, Gusa NL, Finck GK, Johnson C, Goldberg RM (1991) Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. J Clin Oncol 9:449–452
7. Roth BJ, Sledge GW, Williams SD, Meyer SC, Ansari R, Fisher WB (1991) Methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic breast cancer. Cancer 68:248–252
8. Carmo-Perrira J, Costa FO, Miles DW, Henrigues E, Richards MA, Rubens RD (1991) High-dose epirubicin as primary chemotherapy in advanced breast carcinoma; a phase II study. Cancer Chemother Pharmacol 27:394–396
9. Reimann HA, deBerardinis CT (1949) Periodic (cyclic) neutropenia, an entity. Blood 4:1109–1116
10. Hammond WP, Price TH, Souza LM, Dale DC (1989) Treatment of cyclic neutropenia with granulocyte colony-stimulating factor. New Engl J Med 320:1306–1311
11. Nicola NA, Metcalf D (1981) Biochemical properties of differentiation factors for murine myelomonocytic leukemia cells in organ conditioned media-separation from colony-stimulating factor. J Cell Physiol 109:253–264
12. Souza LM, Boone TC, Gabrilove J, Lai PH, Zsebo KM, Murdock DC, Chazin VR, Bruszewski J, Lu H, Chen KK, Barendt J, Platzer E, Moore MAS, Mertelsmann R, Welte K (1986) Recombinant human granulocyte colony-stimulating factor: effects on normal and leukemic myeloid cells. Science 232:61–65
13. Bronchud MH, Scarffe JH, Thatcher N, Crowther D, Souza LM, Alton MK, Testa NG, Dexter TM (1987) Phase I/II study of recombinant human granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for small cell lung cancer. Br J Cancer 56:809–813
14. Morstyn G, Campbell L, Souza LM, Alton NK, Keech J, Green M, Sherdan W, Metcalf D (1988) Effect of granulocyte colony-stimulating factor on neutropenia induced by cytotoxic chemotherapy. Lancet 1:667–672
15. Hanada T, Ono I (1990) Disappearance of neutropenia oscillation in a child with cyclic neutropenia after treatment with recombinant human granulocyte colony-stimulating factor. Eur J Haematol 45:181–182
16. Freund MRF, Luft S, Shoeber C, Heussner P, Schrezenmaier H, Porzsolt F, Welte K (1990) Differential effect on GM-CSF and G-CSF in cyclic neutropenia. Lancet 1:336
17. Gabrilove JL, Jakubowski A, Scher H, Sternberg C, Wong G, Grous J, Yagoda A, Fain K, Moore MAS, Clarkson B, Oettgen HF, Alton K, Welte K, Souza L (1988) Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. New Engl J Med 318:1414–1422
18. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
19. Oheda M, Hase S, Ono M, Ikenaga T (1988) Structure of the sugar chains of recombinant human granulocyte colony-stimulating factor produced by Chinese hamster ovary cells. J Biochem 103:544–546
20. Asano S (1991) Human granulocyte colony-stimulating factor: Its basic aspects and clinical applications. Am J Pediatr Hematol Oncol 13:400–413
21. Sonis ST (1985) Oral complications of cancer chemotherapy. In: DeVita VT Jr, Hellman S, Rosenberg SA (eds) Cancer: principles and practice of oncology, 2nd edn. Lippincott, Philadelphia, pp 2014–2021
22. Yamamoto T, Yoneda K, Ueta E, Hirota J, Osaki T (1991) Serum cytokine levels in patients with oral mucous membrane disorders. J Oral Pathol Med 20:275–279
23. Sternberg CN, Yagoda A, Scher HI, Watson RC, Herr HW, Morse MJ, Sogani PC, Vaughan ED, Bander N, Weiselberg LR, Geller N, Hollander PS, Lipperman R, Fair WR, Whitmore WF (1988) M-VAC (methotrexate, vinblastine, doxorubin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 139:462–469
24. Wingard JR, Niehaus CS, Peterson DE, Jones RJ, Piantadosi S, Levin LS, Saral R, Santos GW (1991) Oral mucositis after bone marrow transplantation: a marker of treatment toxicity and predictor of hepatic veno-occlusive disease. Oral Surg Oral Med Oral Pathol 72:419–424
25. Kostmann R (1956) Infantile genetic agranulocytosis (agranulocytosis infantilis hereditaria): a new recessive lethal disease in man. Acta Paediatr [Suppl] 105:1–78

26. Speat TH, Dameshe KW (1952) Chronic hypoplastic neutropenia. Am J Med 13:35–45
27. Platzer E, Welte K, Gabrilove J, Lu L, Harris P, Mertelsmann R, Moore MAS (1985) Biological activities of human pluripotent hematopoietic colony-stimulating factor on normal and leukemic cells. J Exp Med 162:1788–1801
28. Asano S, Ono M (1987) Human granulocyte colony-stimulating factor: its biological actions and clinical implication. Acta Haematol Jpn 50:106–112
29. Kitagawa S, Yuo A, Souza LM, Saito M, Miura Y, Takaku F (1987) Recombinant human granulocyte colony-stimulating factor enhances superoxide release in human glanulocytes stimulated by the chemotactic peptide. Biochem Biophys Res Commun 144:1143–1146
30. Ohsaka A, Kitagawa S, Sakamoto S, Miura Y, Takanashi N, Takaku F, Saito M (1989) In vivo activation of human neutrophil functions by administration of recombinant human granulocyte colony-stimulating factor in patients with malignant lymphoma. Blood 74:2743–2748