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Efficacy of recombinant human granulocyte-macrophage colony-stimulating factor for chemotherapy-induced leukopenia in patients with non-small-cell lung cancer

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Abstract. To assess the feasibility and efficacy of rhGM-CSF in ameliorating chemotherapy-induced leukopenia in patients with advanced non-small-cell lung cancer, we conducted a double-blind placebo controlled phase III study in a multicenter setting. Patients were eligible if they had cytologically or histologically proven cancer, no prior chemotherapy, stage IIIB or IV disease, an Eastern Cooperativve Oncology Group (ECOG) performance status of 0–2, an age of less than 76 years, and no symptomatic brain metastasis, disseminated bone metastasis, or previous vertebral/pelvic irradiation. The chemotherapy regimen consisted of mitomycin given at 8 mg/m^2 on day 1, cisplatin given at 100 mg/m^2 on day 1, and vindesine given at 3 mg/m^2 i.v. on days 1 and 8 (MVP). If the granulocyte nadir count recorded after the first cycle of MVP was less than 1,000/mm^3, patients were randomly assigned to receive recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) or placebo during the second cycle of MVP. The dose of rhGM-CSF was 125 μg/m^2 given daily s.c. for 14 consecutive days starting on day 2. Of the 52 patients enrolled, 45 were evaluable. The nadir of granulocytes was significantly lower in the placebo group ($P = 0.007$). The period during which the granulocyte count was less than 1,000/mm^3 was significantly longer in the placebo group (median, 6 vs 10 days; $P = 0.04$). The incidence of adverse effects related to rhGM-CSF, such as fever (≥38° C) and skin rash, was significantly higher in the rhGM-CSF group ($P = 0.011$). The rate of response to chemotherapy did not significantly differ between the two groups. In conclusion, rhGM-CSF reduced the duration of chemotherapy-induced granulocytopenia. The clinical usefulness of this agent may be deminished because of the adverse effects encountered when it is used in combination with a moderately myelotoxic chemotherapy regimen.

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Introduction

Recently, recombinant human colony-stimulating factors (rhCSFs) were introduced into cancer chemotherapy trials for the purpose of myeloprotection [4, 27, 31]. Neidhart [25] summarized five reportedly beneficial effects of CSFs used in support of standard chemotherapeutic regimens. In Japan, the use of recombinant human granulocyte-colony-stimulating factor (rhG-CSF) for ameliorating chemotherapy-induced neutropenia has been approved by the Ministry of Public Health and Welfare. However, with regard to recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF), there has been no report of a randomized, double-blind, placebo-controlled trial to evaluate its efficacy in intensive chemotherapy for patients with solid tumors. BI 71.018 is rhGM-CSF made with *Escherichia coli* and was developed by Behringerwerke Co. (Marburg) [15]. The results of a phase I/II study in Japan led to the suggestion that the optimal dose of rhGM-CSF be 125 μg/m^2 daily for the reduction of chemotherapy-induced leukopenia [23].

There is no standard chemotherapy for advanced non-small-cell lung cancer [1, 18]. Although the role of combination chemotherapy has not been established for patients with advanced non-small-cell lung cancer, improvement of physical symptoms has been observed in some patients. New investigational chemotherapy trials using dose-intensive regimens in combination with rhCSFs is a reasonable investigational approach [9, 24, 30, 34].

In this study, we evaluated the utility of rhGM-CSF for ameliorating myelotoxicity in intensive chemotherapy for patients with advanced non-small-cell lung cancer.

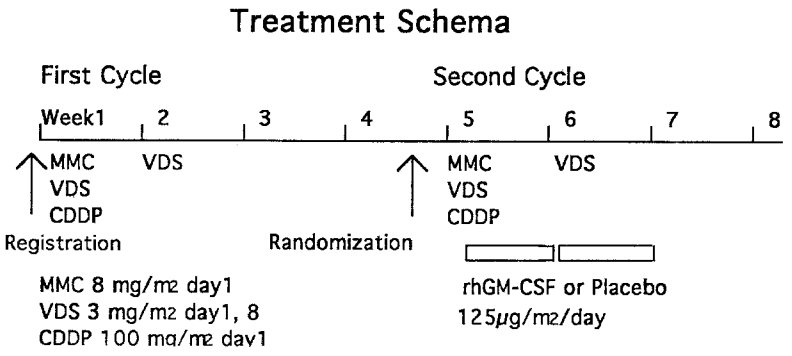


Fig. 1. Treatment schema

Patients and methods

Patients' eligibility. This was a double-blind, placebo-controlled phase III study conducted in a multi-centre setting (see Appendix). Patients with cytologically or histologically proven non-small-cell lung cancer of stage IIIB or IV who had not received prior chemotherapy were accrued to this study. Other eligibility criteria were an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, an age of less than 76 years, serum GOT and GPT levels of less than twice the normal value, a serum creatinine level of <1.5 mg/dl, and normal bone marrow function. Written informed consent was obtained from all patients. Patients with symptomatic brain metastasis, disseminated bone metastasis, and previous vertebral or pelvic irradiation were excluded. The staging methods were as follows: chest X-rays, bronchoscopy, computerized tomography (CT) of the chest, brain CT, abdominal CT or ultrasonography, and bone scan. The same series of examinations were done for restaging of patients after two courses of chemotherapy. Additional clinical examinations were required if disease progression was suspected.

Treatment schedule. The chemotherapy regimen consisted of mitomycin given at 8 mg/m^2 on day 1, cisplatin given at 100 mg/m^2 on day 1, and vindesine given at 3 mg/m^2 i.v. on days 1 and 8 (MVP) and was repeated after 4 weeks. As ancillary therapy, patients received 3,000 ml of supplemental fluid i.v. with diuretics on day 1. If the granulocyte nadir count recorded after the first cycle of MVP was less than 1,000/mm^3, patients were randomly assigned to receive rhGM-CSF or placebo during the second cycle of MVP (Fig. 1). Metoclopramide was given i.v. at 2 mg/kg four times on day 1 as antiemetic therapy. rhGM-CSF (BI 71.018) was supplied by Hoechst Japan Co. (Tokyo). The dose of rhGM-CSF was 125 μg/m^2 given daily s.c. for 14 consecutive days starting on day 2. Patients did not receive rhGM-CSF on the day of chemotherapy.

Concomitant use of steroids and other myeloprotective agents was prohibited. Platelets were transfused when the platelet count decreased below 3×10^4/mm^3 or when any bleeding became prominent. Packed red blood cells were tranfused when the hemoglobin count decreased below 8 g/dl or when anemia became symptomatic. If febrile neutropenic episodes (≥38° C) were observed, antibiotics were given to the patients as indicated. If the WBC rose to $>2\times10^4$/mm^3, the administration of rhGM-CSF was discontinued. Removal from the study was allowed if patients experienced WHO grade 3 or 4 toxicity or objective progression of the disease or if they refused to continue the treatment.

Reporting of laboratory data and evaluation of the results. Eligible patients were registered to the central office by telephone before the first cycle of chemotherapy. If the granulocyte nadir count recorded after the first cycle of MVP was less than 1,000/mm^3, patients were randomly assigned to receive rhGM-CSF or placebo during the second cycle of MVP as shown in Fig. 1. All patients were treated on an inpatient basis. Physical symptoms and vital signs were regularly observed every day. The hematological and biochemical laboratory data were obtained at least twice a week throughout the study period. Aspiration samples of bone marrow were taken before and after the treatment. Chest X-rays were obtained at least every 2 weeks.

The granulocyte nadir count, the median duration of granulocytopenia (WHO grades 3, 4), and the median area under the concentration-time curve (AUC) of the granulocyte count were compared between the two groups as the end points of this study. The AUC of the granulocyte count was calculated in peripheral blood from day 1 until day 21 according to the method of Gurney et al. [14]. Toxicity caused by the administration of rhGM-CSF was reported using WHO criteria. The response to and toxicity of the MVP regimen were also evaluated by WHO criteria. Febrile episodes (≥38° C) occurring without any evidence of infection such as an abnormal chest film, a positive bacterial culture, a response to antibiotics, or septic shock were defined as fever related to rhGM-CSF administration. The clinical efficacy of rhGM-CSF for an individual patient in this protocol setting was scored by each physician participating in this trial on a questionnaire using a 5-point scale prior to unblinding of the results. The 5-point-scale answers consisted of the following items: 5, definitely; 4, moderately; 3, fairly; 2, none; and 1, not evaluable.

Statistical analysis. The balance of the distribution of patients' characteristics between the two groups was examined using the chi-square test. The hematological parameters were compared between the two groups using Wilcoxon's test. The number of patients who showed an increase in granulocyte AUC during the second cycle of MVP as compared with the initial cycle were evaluated between the rhGM-CSF and placebo groups using the sign test. The median survival of patients was calculated beginning from the starting day of the initial chemotherapy using the Kaplan-Meier method. The difference in median survival between the two groups was examined using the log-rank test and the generalized Wilcoxon test.

The clinical efficacy of rhGM-CSF for individual patients as subjectively scored by each physician was analyzed with the questionnaires on the basis of a 5-point scale as mentioned above. A score of 4 or 5 was defined as "useful" and a score of 1 or 2 was defined as "problematic." The significance of any difference was examined using the chi-square test. The efficacy of rhGM-CSF ameliorating leukopenia was also examined among five category groups using the Kruskal-Wallis test.

Results

From December 1990 until December 1991, 52 patients were registered in this study. A total of 45 patients were randomly assigned to two groups before the second course of the chemotherapy (Table 1). Three patients were excluded because of the high absolute granulocyte nadir counts of over 1,000/mm^3 recorded during the first cycle of MVP. One patient with stage I disease was ineligible. Three other patients were excluded from the study because of steroid use during the treatment course. In all, 18 patients were classified as stage IIIB and 27 patients, as stage IV. Overall, 35 patients had not undergone prior surgery. In all, 32 patients had adenocarcinoma. No difference in the patients' characteristics was found between the two groups.

Table 1. Comparison of patients' characteristics

Category	GM (n = 22)	Placebo (n = 23)	P[a]
Sex:			
M	15	13	0.420
F	7	10	
Age (years):			
≥39	0	1	0.088
40–49	6	1	
50–59	8	9	
60–69	3	9	
70–79	5	3	
Body surface area (m^2):			
1.0–1.4	6	9	0.399
1.5–1.9	16	14	
PS (ECOG):			
0–1	18	17	0.806
2	4	6	
Stage:			
IIIB	7	11	0.278
IV	15	12	
Prior surgery:			
None	18	17	0.524
Histology:			
Adenocarcinoma	15	17	0.671
Squamous-cell	4	5	
Large-cell	2	1	
Others	1	0	

[a] Chi-square test

Comparison of hematological toxicities

The median granulocyte nadir count was 540/mm^3 in the rhGM-CSF group and 200/mm^3 in the placebo group (P = 0.007; Fig. 2). The median period during which the granulocyte count was less than 1,000/mm^3 was 6 days in the rhGM-CSF group and 10 days in the placebo group (P = 0.04). The median AUC of the granulocyte count in peripheral blood was 70,532 and 34,085/mm^3 per day, respectively (P = 0.001). With regard to the nadirs of the differentials of peripheral blood cells after the MVP regimen, there was a significant increase in the mean nadir counts of eosinophils in the rhGM-CSF group (P = 0.035).

No significant difference in the nadir count of hemoglobin was noted between the two groups (9.5 ± 1.3 g/dl in the rhGM-CSF group vs 9.4 ± 1.2 g/dl in the placebo group; P = 0.25). There was a significantly earlier decrease in the platelet count to the nadir value in the rhGM-CSF group (median, 10 vs 12 days; P = 0.001). However, no significant difference in the nadir platelet count was observed between the two groups (7.4 ± 4.4×10^4/mm^3 in the rhGM-CSF group vs 7.9 ± 4.8×10^4/mm^3 in the placebo group; P = 0.80). Four patients in the rhGM-CSF group and five patients in the placebo group experienced WHO grades 3 and 4 thrombocytopenia, respectively, and no difference in the volume of platelet transfusion was seen between the two groups.

To assess the myeloprotective effect of rhGM-CSF for the same patients during two sequential courses of the MVP regimen, the change in the granulocyte count AUC was compared between the first and the second cycles. The patients who showed the increase in the granulocyte AUC during the second cycle of MVP as compared with the first cycle included 14 of 20 patients in the rhGM-CSF group as opposed to 3 of 22 patients in the placebo group. In addition, none of the patients in the rhGM-CSF group showed a decrease in granulocyte AUC during the second cycle as compared with the first cycle (P < 0.01), whereas 13 of 22 patients in the placebo group did so (P < 0.05). The quantity of patients who showed an increase in the granulocyte AUC during the second cycle of the MVP regimen was significantly higher in the rhGM-CSF group as compared with the placebo group using the sign test.

Adverse effects

The incidence of adverse effects related to rhGM-CSF, such as fever (≥38° C) and skin rash, was significantly higher in the rhGM-CSF arm (P = 0.001; Table 2). Three patients in each group had infectious episodes (two patients each with pneumonia, sepsis, and abscess) during the treatment course. However, there was no fatal complication.

A comparison of the changes in the laboratory data occurring after the chemotherapy between the rhGM-CSF and the placebo groups revealed significant decreases in the rhGM-CSF group for serum GOT (–16.5 ± 19.2 vs –1.1 ± 18.3 U/ml; P = 0.006), serum lactic dehydrogenase (–88.1 ± 133.2 vs –29.1 ± 70.1 U/ml; P = 0.044), total protein (–0.7 ± 0.5 vs –0.3 ± 0.5 g/dl; P = 0.01), serum albumin (–0.36 ± 0.27 vs –0.07 ± 0.37 mg/dl; P = 0.008), and total cholesterol (–45.7 ± 20.5 vs –15.4 ± 13.0 mg/dl; P = 0.002). However, there was no clinically hazardous change in the absolute values of the blood chemistry parameters in terms of liver or renal function or serum electrolytes

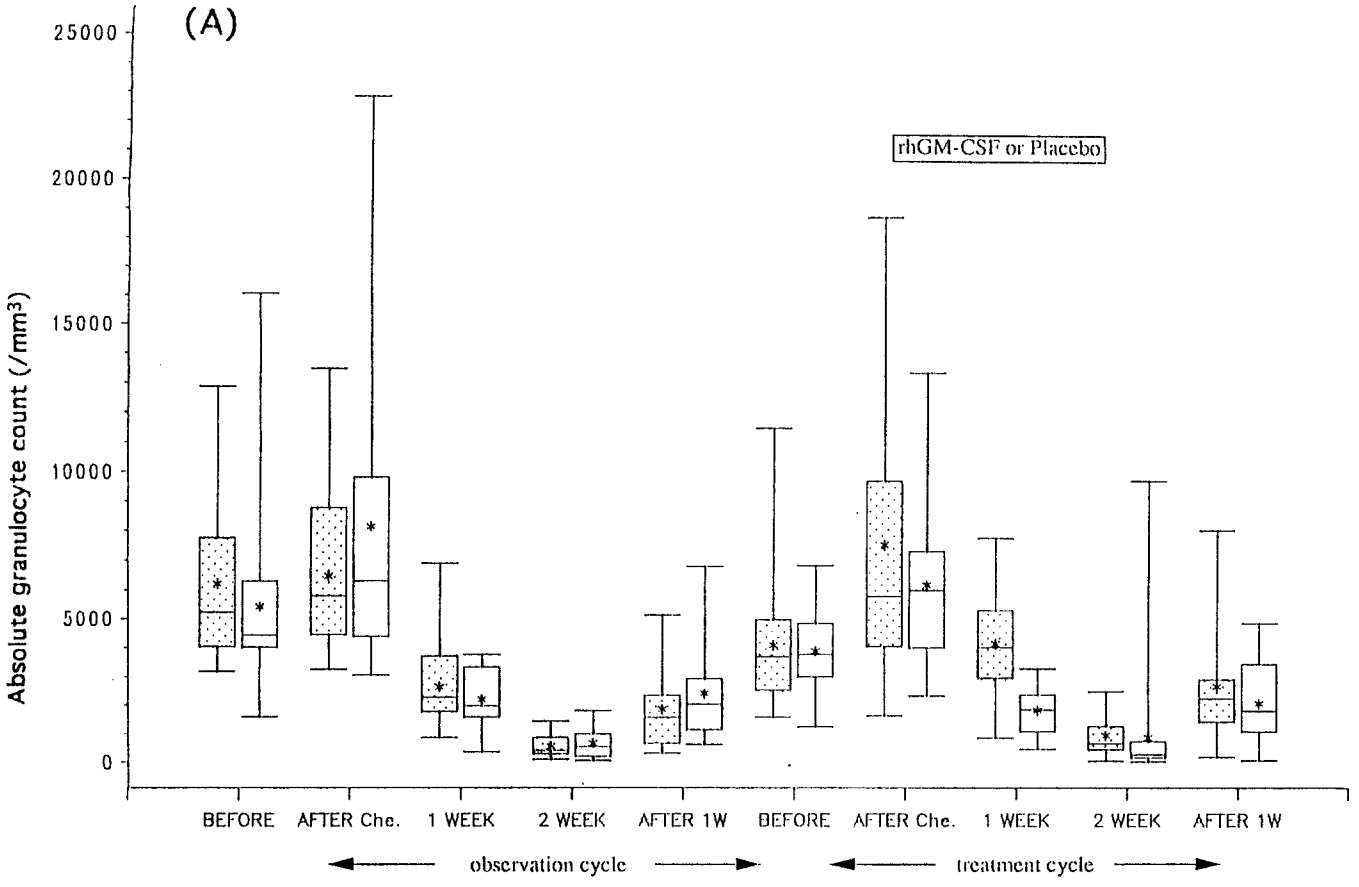
Response to the MVP regimen and survival of patients

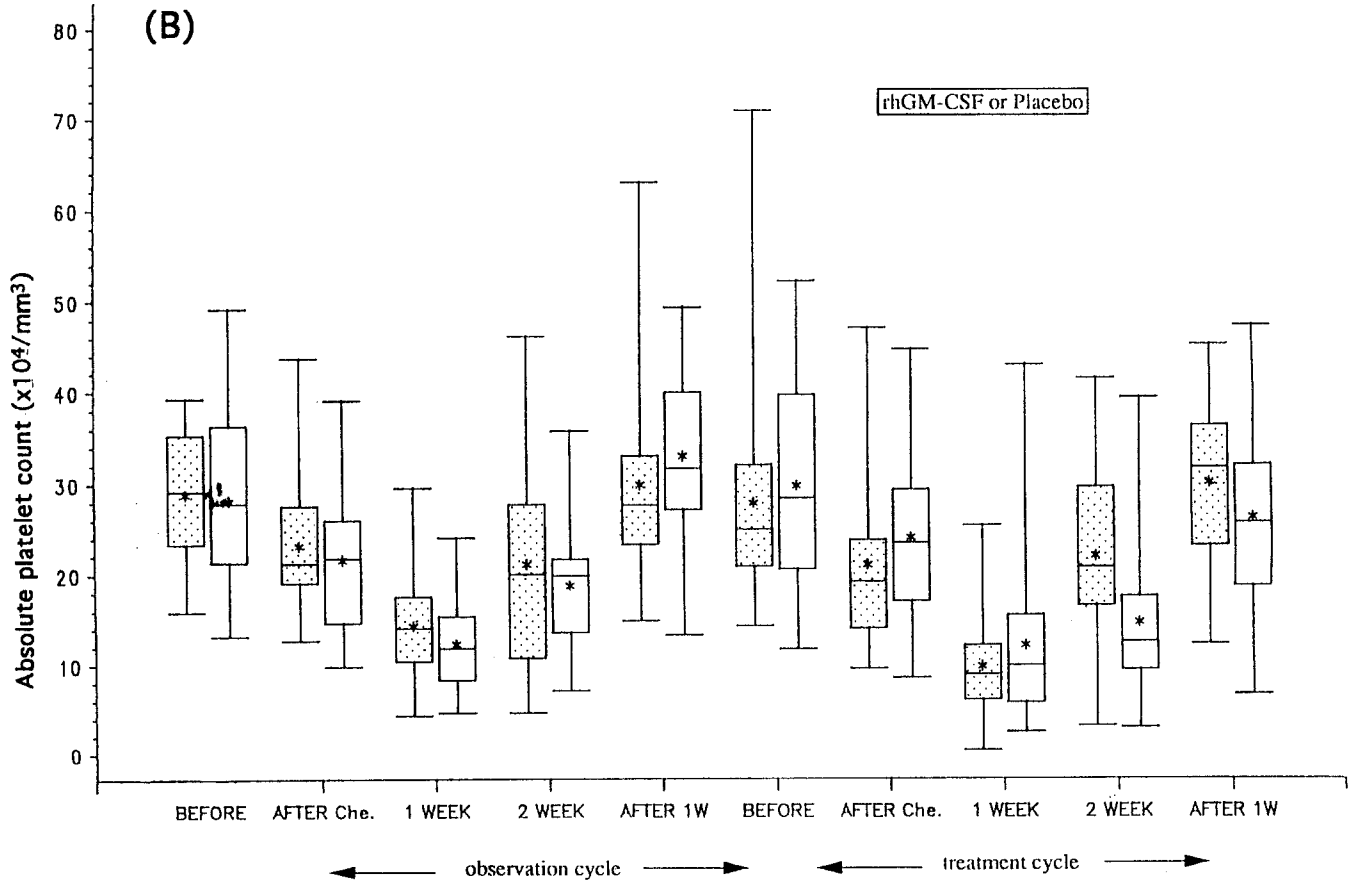
There was no complete response in either group. In all, 10 of 22 patients in the rhGM-CSF group and 6 of 23 patients in the placebo group achieved a partial response; the re-

Table 2. Comparison of adverse effects observed during chemotherapy with or without rhGM-CSF

Adverse effects	Number of patients[a]		P[b]
	GM (n = 22)	Placebo (n = 23)	
Overall no. of patients	15	4	0.001
Chest pain	2	0	0.233
Induration of injection sites	3	0	0.109
Fever (≥38° C)	6	1	0.047
Skin rash	4	0	0.049
Vomiting (grades 3, 4)	4	0	0.049
Increase in serum GOT, GPT	0	3	0.489

[a] Number of patients who showed any adverse effect
[b] Chi-square test


(A)
rhGM-CSF or Placebo
Absolute granulocyte count (/mm³)
25000
20000
15000
10000
5000
0
BEFORE
AFTER Che.
1 WEEK
2 WEEK
AFTER 1W
BEFORE
AFTER Che.
1 WEEK
2 WEEK
AFTER 1W
observation cycle
treatment cycle


(B)
rhGM-CSF or Placebo
Absolute platelet count (x10⁴/mm³)
80
70
60
50
40
30
20
10
0
BEFORE
AFTER Che.
1 WEEK
2 WEEK
AFTER 1W
BEFORE
AFTER Che.
1 WEEK
2 WEEK
AFTER 1W
observation cycle
treatment cycle

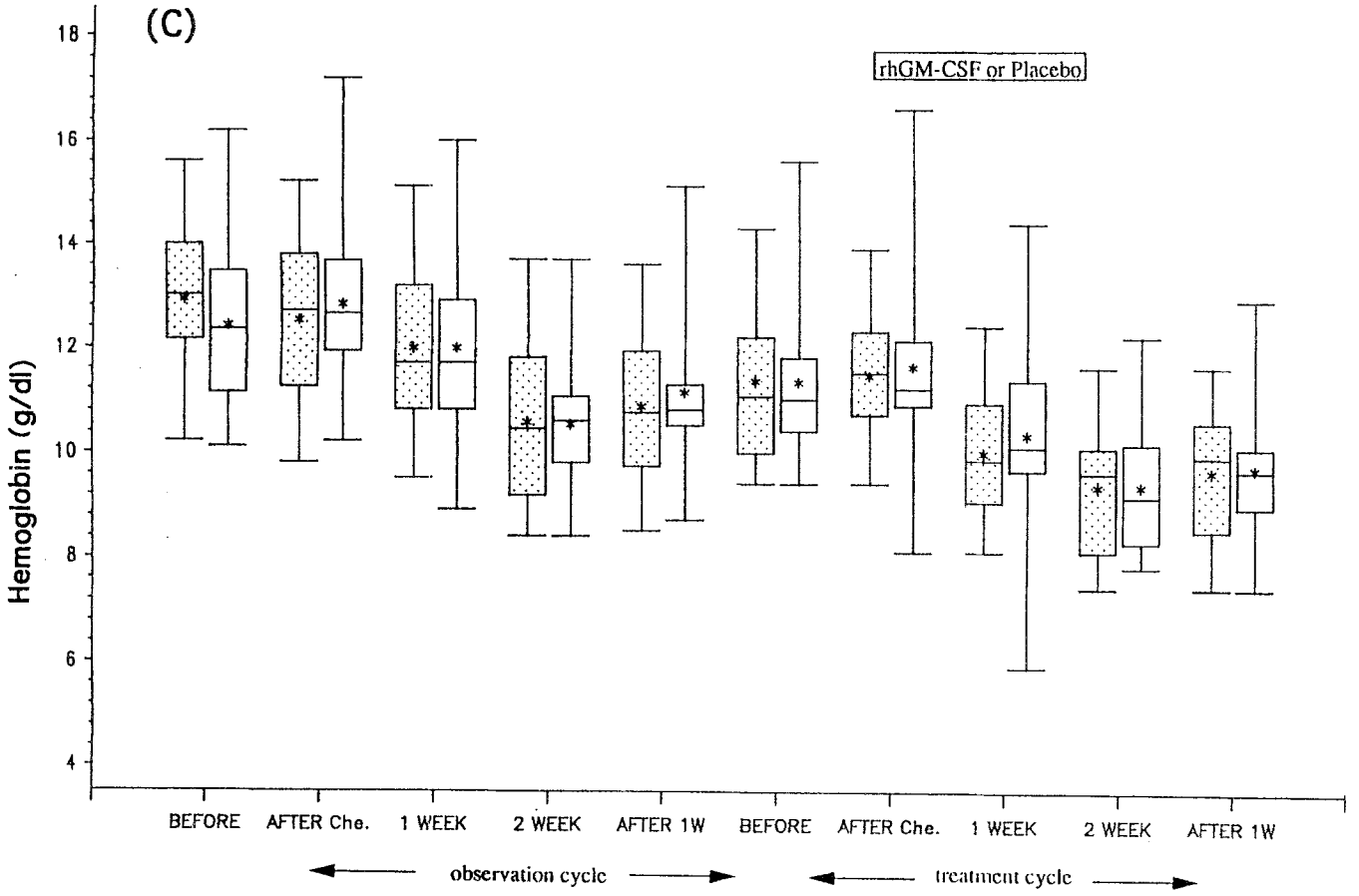


Fig. 2A–C. Changes in hematological parameters of the patients before and after chemotherapy. **A** Changes in absolute granulocyte count. **B** Changes in absolute platelet count. **C** Changes in hemoglobin. *, Mean value; ———, median value; ▨, patients receiving rhGM-CSF (125 μg/m², s.c.); □, patients receiving placebo

sponse rate was 45% and 26%, respectively, and the 95% confidence interval was 24%–66% and 8%–44%, respectively. The rate of response to the MVP regimen did not significantly differ between the two groups ($P = 0.20$). A total of 8 patients in the rhGM-CSF group and 12 patients in the placebo group showed no change. Two patients in the former group and one patient in the latter group experienced progressive disease. Two and four patients, respectively, were not evaluable in the two groups. The median survival of all patients included in this study was 300 days.

Subjective evaluation by participating physicians

In 8 patients in the rhGM-CSF group (36%) and 3 patients in the placebo group (13%), the scheduled administration of trial drug was discontinued during chemotherapy-induced neutropenia ($P = 0.21$; Table 3). In four of eight patients it was discontinued because of adverse effects of rhGM-CSF such as induration of the injection site and skin rash, whereas none of the patients in the placebo group developed such signs. Two of eight patients in the rhGM-CSF groups and one patient in the placebo group refused to continue receiving the trial drug because of nausea and vomiting or fatigue. In one patient in each group it was discontinued because of protocol violation. As shown in Table 3, the clinical efficacy of rhGM-CSF for individual patients as subjectively scored by each physician prior to the opening of the results could not be demonstrated ($P = 0.091$), and the incidence of adverse effects was significantly higher in the rhGM-CSF group ($P = 0.004$).

Discussion

The ameliorating effect of rh granulocyte-CSF (rhG-CSF) and rhGM-CSF in patients with chemotherapy-induced myelotoxicity has recently been extensively studied. Both rhCSFs have proved to be effective in reducing myelo-

Table 3. Clinical efficacy of the administration of rhGM-CSF or placebo for the individual patient scored by each physician participating in this trial

	Number of patients		
	GM ($n = 22$)	Placebo ($n = 23$)	P^a
Clinical usefulness in ameliorating leukopenia[b]	6	4	0.425
Problems of side effects	6	0	0.004

The questionnaires used a 5-point scale, whereby treatment of patients given a score of 4 or 5 was defined as useful and that of patients assigned score of 1 or 2 was defined as problematic

[a] Chi-square test

[b] Comparison between 5 category-groups, $P = 0.091$ (Kruskal-Wallis test)

toxicity by shortening the duration of neutropenia and decreasing both infection and the duration of hospitalization [5, 6, 11–13, 16]. However, the double-blind placebo-controlled study that was recently reported by Khawaja et al. [20] failed to show an improvement in the clinical outcome with the use of rhGM-CSF in patients undergoing high-dose chemotherapy plus autologous bone marrow transplantation. Gurney et al. [14] observed that the nadir induced by the moderately intensive chemotherapy could not be shortened even with rhGM-CSF in patients with small-cell lung cancer, although their study was a small-sized cross-over trial. rhG- and rhGM-CSF have been approved for clinical use in many countries. However, no consensus has been reached concerning the use of rh-CSFs in combination with intensive chemotherapy in patients with advanced cancer. We could not analyze the cost-effective comparison between the two groups in this study, since all patients were treated on an inpatient basis. We think that the use of rh-CSFs should be reserved for patients who are expected to gain a survival benefit from intensive chemotherapy. The use of rh-CSF in combination with a moderately myelotoxic regimen remains investigational in patients with various solid tumors.

As compared with rhG-CSF, rhGM-CFS is an inducible protein that occurs at increased levels in peripheral blood during inflammatory reactions and has a broad spectrum of biological activities. This may partly be the reason for the higher incidence of adverse effects noted in patients receiving this trial drug. The present study was designed in accordance with information available in January 1990, including preliminary results of phase II trials conducted by many groups. rhG-CSF was effective in shortening the duration of granulocytopenia and increasing the nadir leukocyte count at a dose of 100 μg/m^2 or 3 μg/kg when given by both the i.v. and the s.c. route in several phase I or I/II studies [19, 21, 32, 33]. At the higher dose level of rhGM-CSF, capillary leak syndromes and venous thrombosis were observed. Emminger et al. [8] reported that the capillary leak syndrome occurred even at the low dose level of rhGM-CSF (250 μg/m^2) in a patient undergoing high-dose chemotherapy plus autologous bone marrow transplantation. The dose of rhGM-CSF used in our study was almost 50% lower than those given in other studies, but the present dose was suggested from a phase I/II study in Japan [23]. This discrepancy may represent a racial difference in the tolerance/toxicity of this agent. Even at this low dose of rhGM-CSF, most patients experienced adverse effects.

The choice of rhCSFs in combination with intensive chemotherapy will depend on the role of the CSF in the treatment schedule. The combination use of rhGM-CSF in phase I studies of high-dose chemotherapy has not been fully supported. Recently, Rusthoven et al. [29] and O'Dwyer et al. [26] showed that rhGM-CSF apparently enhanced chemotherapy-induced hematotoxicity, especially thrombocytopenia. They could not achieve dose escalation of chemotherapeutic agents because of severe thrombocytopenia. Hoekman et al. [17] demonstrated that rhGM-CSF could not support the myelotoxicity of multicycle chemotherapy in patients with advanced breast cancer. In a Southwest Oncology Group combined-modality study in patients with limited small-cell lung cancer, Bunn et al. [3] reported a significantly greater degree of thrombocytopenia in the rhGM-CSF group. Although our study could not clarify the relationship between the schedule of administration of rhGM-CSF and the degree of thrombocytopenia, concurrent use of rh-CSFs and an intensive myelotoxic regimen should be avoided.

The strategy involving the combined use of rhCSFs such as interleukin 3 (IL-3) plus GM-CSF [2, 10, 28] and evaluation of the clinical benefit of using rhCSF-induced peripheral progenitor cells in intensive cancer treatment [7, 22, 35] clearly warrant study for the effective amelioration of chemotherapy-induced myelotoxicity.

In conclusion, rhGM-CSF did reduce the duration of chemotherapy-induced granulocytopenia and ameliorate the nadir granulocyte count. The incidence of adverse effects such as fever, induration of the injection site, and skin rash was significantly higher in patients receiving rhGM-CSF. The clinical usefulness of this agent could not be demonstrated because of the adverse effects observed during its use in combination with a moderately myelotoxic chemotherapy regimen.

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References

1. Bonomi PD, Finkelstein DM, Ruckdeschel JC, Blum RH, Green MD, Mason B, Hahn R, Tormey DC, Harris J, Comis R, Glick J (1989) Combination chemotherapy versus single agents followed by combination chemotherapy in stage IV non-small-cell lung cancer: a study of the Eastern Cooperative Oncology Group. J Clin Oncol 7: 1602–1613
2. Brugger W, Frisch J, Schulz G, Pressler K, Mertelsmann R, Kanz L (1992) Sequential administration of interleukin-3 and granulocyte-macrophage colony-stimulating factor following standard-dose combination chemotherapy with etoposide, ifosfamide, and cisplatin. J Clin Oncol 10: 1452–1459
3. Bunn PA, Crowley J, Hazuka M (1991) A randomized study of VP-16/cisplatin/chest RT ± GM-CSF in limited stage small cell lung cancer (SCLC): preliminary results of a Southwest Oncology Group (SWOG) study. Lung Cancer 7 [Suppl]: 139
4. Crawford J, Green MR (1992) The role of colony stimulating factors as an adjunct to lung cancer chemotherapy: a commentary. Lung Cancer 8: 153–158
5. Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, Kris M, Grous J, Picozzi V, Rausch G, Smith R, Gradishar W, Yahanda A, Vincent M, Stwart M, Glaspy J (1991) Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 325: 164–170
6. De Vries EGE, Biesma B, Willemse PHB, Mulder NH, Stern A, Aalders JG, Vellenga E (1991) A double-blind placebo-controlled study with granulocyte-macrophage colony-stimulating factor during chemotherapy for ovarian carcinoma. Cancer Res 51: 116–122

7. Elias AD, Ayash L, Anderson KC, Hunt M, Wheeler C, Schwartz G, Tepler I, Mazanet R, Lynch C, Pap S, Pelaez J, Reich E, Critchlow J, Demetri G, Bibbo J, Schnipper L, Griffin JD, Frei E III, Antman K (1992) Mobilization of peripheral blood progenitor cells by chemotherapy and granulocyte-macrophage colony-stimulating factor for hematologic support after high-dose intensification for breast cancer. Blood 79: 3036–3044
8. Emminger W, Emminger-Schmidmeier W, Peters C, Susani M, Hawliczekm R, Hocker P, Gadner H (1990) Capillary leak syndrome during low dose granulocyte-macrophage colony-stimulating factor (rhGM-CSF) treatment of a patient in a continuous febrile state. Blut 61: 219–221
9. Gandara DR, Wold H, Perez EA, Deisseroth AB, Doroshow J, Meyers F (1989) Cisplatin dose intensity in non-small cell lung cancer: phase II results of a day 1 and day 8 high-dose regimen. J Natl Cancer Inst 81: 790–794
10. Ganser A, Lindemann A, Ottmann OG, Seipelt G, Hess U, Geissler G, Kanz L, Frisch J, Schulz G, Herrmann F, Mertelsmann R, Hoelzer D (1992) Sequential in vivo treatment with two recombinant human hematopoietic growth factors (interleukin-3 and granulocyte-macrophage colony-stimulating factor) as a new therapeutic modality to stimulate hematopoiesis: results of a phase I study. Blood 79: 2583–2591
11. Gianni AM, Bregni M, Siena S, Orazi A, Stern AC, Gandola L, Bonadonna G (1990) Recombinant human granulocyte-macrophage colony-stimulating factor reduces hematologic toxicity and widens clinical applicability of high-dose cyclophosphamide treatment in breast cancer and non-Hodgkin's lymphoma. J Clin Oncol 8: 768–778
12. Gorin NC, Coiffier B, Hayat M, Fouillard L, Kuentz M, Fleisch M, Colombat P, Boivin P, Slavin S, Philip T (1992) Recombinant human granulocyte-macrophage colony-stimulating factor after high-dose chemotherapy and autologous bone marrow transplantation with unpurged and purged marrow in non-Hodgkin's lymphoma: a double-blind placebo-controlled trial. Blood 80: 1149–1157
13. Gulati SC, Bennett CL (1992) Granulocyte-macrophage colony-stimulating factor (GM-CSF) as adjunct therapy in relapsed Hodgkin's lymphoma. Ann Intern Med 116: 177–182
14. Gurney H, Anderson H, Radford J, Potter MR, Swindell R, Steward W, Kamthan A, Chang J, Weiner J, Thatcher N, Crowther D (1992) Infection risk in patients with small cell lung cancer receiving intensive chemotherapy and recombinant human granulocyte-macrophage colony-stimulating factor. Eur J Cancer 28: 105–112
15. Herrmann F, Schulz G, Lindemann A, Meyenburg W, Oster W, Krumwieh D, Mertelsmann R (1989) Hematopoietic responses in patients with advanced malignancy treated with recombinant human granulocyte-macrophage colony-stimulating factor. J Clin Oncol 7: 159–167
16. Herrmann F, Schulz G, Wieser M, Kolbe K, Nicolay U, Noack M, Lindemann A, Metersmann R (1990) Effect of granulocyte-macrophage colony-stimulating factor on neutropenia and related morbidity induced by myelotoxic chemotherapy. Am J Med 88: 619–624
17. Hoekman K, Wagstaff J, Groeningen CJ van, Vermorken JB, Boven E, Pinedo HM (1991) Effect of recombinant human granulocyte-macrophage colony-stimulating factor on myelosuppression induced by multiple cycles of high-dose chemotherapy in patients with advanced breast cancer. J Natl Cancer Inst 83: 1546–1553
18. Ihde DC (1992) Chemotherapy of lung cancer. N Engl J Med 327: 1434–1441
19. Jost LM, Pichert G, Stahel RA (1990) Placebo controlled phase I/II study of subcutaneous GM-CSF in patients with germ cell tumors undergoing chemotherapy. Ann Oncol 1: 439–442
20. Khawaja A, Linch DC, Goldstone AH, Chopra R, Marcus RE, Wimperis JZ, Russel NH, Haynes AP, Milligan DW, Leyland MJ, Winfield DA, Hancock BW, Newland A, Durrant ST, Devereux S, Roitt S, Collins M, Hudson GV (1992) Recombinant human granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for malignant lymphoma: a British National Lymphoma Investigation double-blind, placebo-controlled trial. Br J Haematol 82: 317–323
21. Leischke GJ, Maher D, Cebon J, O'Connor M, Green M, Sheridan W, Boyd A, Rallings M, Bonnem E, Metcalf D, Burgess AW, McGrath K, Fox RM, Morstyn G (1989) Effects of bacterially synthesized recombinant human granulocyte-macrophage colony-stimulating factor in patients with advanced malignancy. Ann Intern Med 110: 357–364
22. Lowry PA, Tabbara IA (1992) Peripheral hematopoietic stem cell transplantation: current concepts. Exp Hematol 20: 937–942
23. Miwa S, Shibata A, Kaneko T, Moriyama Y, Kaku K, Ishida Y, Takahashi M (1992) Phase I/II study of recombinant human granulocyte-macrophage colony-stimulating factor in patients with advanced malignancy. Acta Haematol (Basel) 87: 22–28
24. Murray N, Osoba D, Shah A, Page R, Karsai H, Little C (1991) Brief intensive chemotherapy for metastatic non-small-cell lung cancer: a phase II study of the weekly CODE regimen. J Natl Cancer Inst 83: 190–194
25. Neidhart JA (1992) Hematopoietic colony-stimulating factors, uses in combination with standard chemotherapeutic regimens and in support of dose intensification. Cancer [Suppl] 70: 913–920
26. O'Dwyer PJ, Lacreta FP, Schilder P, Nash S, McAleer C, Miller LL, Hudes GR, Ozols R (1992) Phase I trial of thiotepa in combination with recombinant human granulocyte-macrophage colony-stimulating factor. J Clin Oncol 10: 1352–1358
27. Onge JS, Jacobson RJ (1992) The role of hematopoietic growth factors in the treatment of neoplastic diseases. Semin Hematol 29: 53–63
28. Orazi A, Cattoretti G, Schiro R, Siena S, Bregni M, Di Nicola M, Gianni A (1992) Recombinant human interleukin-3 and recombinant human granulocyte-macrophage colony-stimulating factor administered in vivo after high-dose cyclophosphamide cancer chemotherapy: effect on hematopoiesis and microenvironment in human bone marrow. Blood 79: 2610–2619
29. Rusthoven J, Levin L, Eisenhauer E, Mazurka J, Carmichael J, O'Connell G, Bryson P, Hirte H, Koski B (1991) Two phase I studies of carboplatin dose escalation in chemotherapy-naive ovarian cancer patients supported with granulocyte-macrophage colony-stimulating factor. J Natl Cancer Inst 83: 1748–1753
30. Saito Y, Mori K, Tominaga k, Yokoi K, Miyazawa N (1992) Phase II study of cisplatin as a 5-day continuous infusion with vindesine plus recombinant human granulocyte-colony-stimulating factor in the treatment of advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 31: 81–84
31. Scarffe JH (1991) Emerging clinical uses of GM-CSF. Eur J Cancer 27: 1493–1504
32. Schwarz GK, Collins JJ, Galazka A, Nessi PA, Lehrer D, Baldwin Y, Mandeli J, Holland JF (1992) Phase I study of subcutaneously administered bacterially-synthesized recombinant human granulocyte macrophage colony-stimulating factor. Eur J Cancer 28: 470–473
33. Steward WP, Scraffe JH, Austin R, Bonnem E, Thatcher N, Morgenstern G, Crowther D (1989) Recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF) given as daily short infusions – a phase I dose-toxicity study. Br J Cancer 59: 142–145
34. Takada M, Fukuoka M, Ariyoshi Y, Furuse K, Niitani H, Ota K, Motomiya M, Hasegawa K, Tominaga K, Kuriyama T, Yoshida K, Kimura H, Kurita Y, Nakajima S, Nakai J, Ohta M, Yamamoto H (1992) The use of granulocyte colony-stimulating factor to shorten the interval between cycles of mitomycin C, vindesine and cisplatin chemotherapy in non-small-cell lung cancer. Cancer Chemother Pharmacol 31: 182–186
35. Vadhan-Raj S, Broxmeyer HE, Hittelman W, Papadopoulos NE, Chawla SP, Fenoglio C, Cooper S, Buescher ES, Frenkck RW, Holian A, Perkins R, Scheule RK, Gutterman JU, Salem P, Benjamin RS (1992) Abrogating chemotherapy-induced myelosuppression by recombinant granulocyte-macrophage colony-stimulating factor in patients with sarcoma: protection at the progenitor cell level. J Clin Oncol 10: 1266–1277