Cancer Chemother Pharmacol (1992) 31: 182–186

Cancer Chemotherapy and Pharmacology

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*

Minoru Takada[1], Masahiro Fukuoka[1], Yutaka Ariyoshi[2], Kiyoyuki Furuse[3], Hisanobu Niitani[4], Kazuo Ota[5], Masakichi Motomiya[6], Kouichi Hasegawa[7], Keigo Tominaga[8], Takayuki Kuriyama[9], Kiyokazu Yoshida[10], Hitoshi Kimura[11], Yuzo Kurita[12], Shigenori Nakajima[13], Jun Nakai[14], Mituo Ohta[15], and Hidehiko Yamamoto[16]

[1] Osaka Prefectural Habikino Hospital; [2] Aichi Cancer Center; [3] Kinki-Central Hospital for Chest Disease; [4] Nippon Medical School; [5] Nagoya Memorial Hospital, [6] Tohoku University, [7] Tuboi Hospital; [8] Tochigi Cancer Center; [9] Chiba University; [10] Saitama Cancer Center; [11] Komagome Hospital; [12] Niigata Cancer Center; [13] Kinki University; [14] Kobe General Central Hospital; [15] National Kyushu Cancer Center; [16] Iizuka Hospital

Received 7 May 1992/Accepted 3 August 1992

Summary. We investigated the possibility of shortening the interval between courses of the commonly prescribed 28-day MVP (mitomycin C, vindesine, and cisplatin) regimen in patients with non-small-cell lung cancer (NSCLC). We conducted a nonrandomized phase II study using recombinant human granulocyte colony-stimulating factor (G-CSF, Chugai) to explore the possibility of shortening the cycle length to 21 days and compared the results with those obtained in historical controls who had received the standard 28-day regimen. A total of 40 patients, 37 of whom were evaluable, were entered in the 21-day treatment group of the trial and were compared with 38 historical controls who had received standard 28-day cycles of MVP at our institution. Patients in the 21-day group received mitomycin C at 8 mg/m^2 on day 1, vindesine at 3 mg/m^2 on days 1 and 8, and cisplatin at 80 mg/m^2 on day 1, with the schedule being repeated every 21 days. Controls had received the same regimen, albeit at 28-day intervals. G-CSF was given s.c. to the patients in the 21-day group at a daily dose of 2 μg/kg from day 2 to day 21 of every MVP cycle. The administration of G-CSF to these patients accelerated neutrophil recovery as compared with that observed in the historical controls. Significant differences were found between the two groups in terms of mean neutrophil nadirs (2666/μl in the first cycle and 1369/μl in the second for the G-CSF group vs 416/μl in the first cycle and 685/μl in the second cycle for the control group; $P < 0.0001$) and the mean duration of neutropenia (≤ 1000/μl; 1.0 day in the first cycle and 1.7 days in the second for the G-CSF group vs 8.0 days in the first cycle and 6.9 days in the second for the control group; $P < 0.0001$). This enabled 32 (86%) of 37 patients in the G-CSF group to complete ≥ 2 cycles on schedule. In 10 patients, the bone marrow aspirates taken after G-CSF administration showed increases in band neutrophil and myelocyte percentages. In conclusion, MVP treatment of patients with NSCLC at 21-day intervals is possible with the support of G-CSF.

Introduction

Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancers. At present, combination chemotherapy is the widely accepted treatment modality for patients with advanced NSCLC, although the results have not been as encouraging as had first been hoped. Although modest progress has been made in the treatment of patients with unresectable NSCLC, especially since the introduction in the 1980s of regimens containing platinum and vinca alkaloids [3], there has thus far been no evidence of a prolongation of survival. Various strategies to prolong patient survival have been devised. One of the most attractive is thought to be dose-intensive chemotherapy, in which chemotherapeutic agents are given at close intervals [4]. However, it has been well demonstrated that dose-intensive chemotherapy results in bone marrow toxicity and that the control of this complication is of import in its use. Chemotherapy-induced thrombocytopenia can be ameliorated by platelet transfusions and thus does not present a major problem, leaving neutropenia as the most important factor begging a solution. Bodey et al. [1] reported that the depth and duration of neutropenia was the most important causative factor in fever and infection. From this observation, it may be surmised that the control of leukopenia is the key to success in dose-intensive chemotherapy.

With the discovery of human granulocyte colony-stimulating factor (G-CSF) [11, 12], new possibilities for the control of neutropenia have arisen. The excellent recovery of absolute neutrophil counts (ANC) in primates that had received cytotoxic treatment together with G-CSF [15] gave impetus to the use of the latter in human clinical trilas,

* This study was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare (62S-1) and by the Chugai Pharmaceutical Company

Correspondence to: Masahiro Fukuoka, Osaka Prefectural Habikino Hospital, 3-7-1 Habikino, Habikino City, Osaka 583, Japan

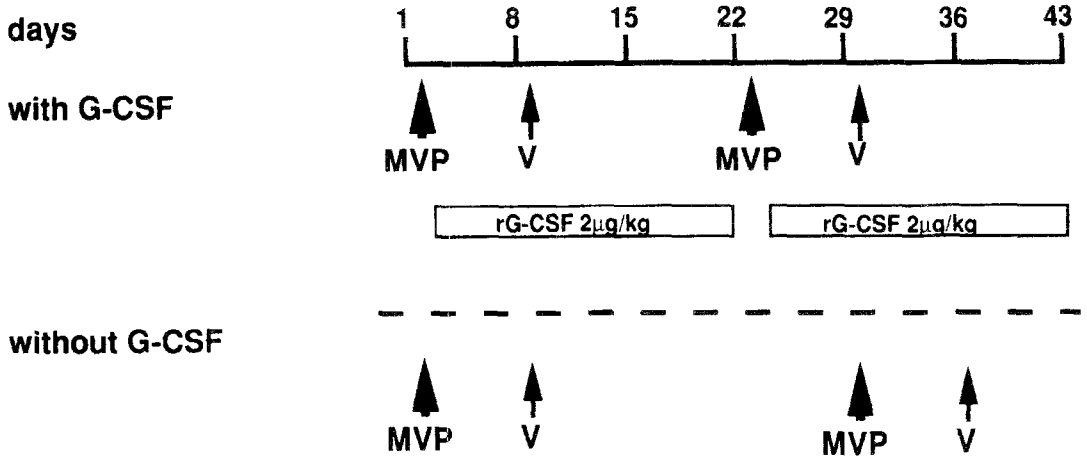

Fig. 1. Study design. Mitomycin C (*M*) was given i. v. at 8 mg/m^2 on day 1, vindesine (*V*) was given i. v. at 3 mg/m^2 on days 1 and 8, and cisplatin (*P*) was given by drip infusion at 80 mg/m^2 on day 1

and with the availability of recombinant products in 1986 [13], its clinical use in humans became a reality. Drawing on the possibility of using recombinant G-CSF to alleviate neutropenia and thus to shorten the length of chemotherapy cycles used in the treatment of NSCLC, we designed the present study to determine whether G-CSF would enable the enrolled patients to receive 21-day cycles of mitomycin C, vindesine, and cisplatin (MVP) therapy at the full dose and on schedule. We compared the hematologic recovery during G-CSF therapy with the results obtained in our historical controls who had been given the same regimen at 28-day intervals for the treatment of NSCLC [7].

Patients and methods

A total of 40 patients with histologically confirmed NSCLC were studied between April 1989 and November 1989 after they had given their informed consent. To be eligible, patients had to be ≤75 years of age and to have a total leukocyte count of ≥4,000/μl, a platelet count of ≥100,000/μl, a predicted life expectancy of at least 3 months, adequate renal and hepatic function, a serum creatinine level of ≤1.5 mg/ml, GOT and/or GPT values of <2 times the upper normal levels, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2. Patients who had received prior chemotherapy were also eligible, provided that the last course has been completed by >4 weeks prior to their entry into the present study.

Of the patients with inoperable NSCLC who had been included in a three-arm randomized trial of vindesine and cisplatin versus mitomycin, vindesine, and cisplatin versus etoposide and cisplatin alternating with vindesine and mitomycin, 38 had been treated with the same MVP regimen on the conventional 28-day schedule between June 1986 and April 1988 at the Osaka Prefectural Habikino Hospital [7]. Therefore, these 38 patients served as historical controls in the present study.

The hematologic examinations included total counts of red blood cells, thrombocytes, and white blood cells with differential granulocyte counts. These examinations were routinely performed twice a week, but when the WBC fell below 1,000/μl, they were carried out daily until these values recovered to ≥1,000/μl. Bone marrow samples were obtained by aspiration from the posterior iliac crest. Bone marrow smears were prepared prior to treatment and on the last day of the first cycle of G-CSF administration and were stained using May-Giemsa. Differential cell counts were done by examining 1,000 white cells.

All patients who were entered in this trial received chemotherapy consisting of 80 mg/m^2 cisplatin given on day 1, 3 mg/m^2 vindesine given on days 1 and 8, and 8 mg/m^2 mitomycin C given on day 1. The regimen was repeated for at least two cycles at 21-day intervals in the G-CSF group and at 28-day intervals in the control group. Patients who responded to the treatment were continued on chemotherapy until they developed progressive disease or major toxicity. For patients whose disease either did not change or progressed, the chemotherapy was discontinued. The study design is shown in Fig. 1.

G-CSF (rG-CSF, Chugai) was supplied by Chugai Pharmaceutical Company, Tokyo, Japan. G-CSF is a glycoprotein (relative mol. wt., 19,000 Da) composed of 174 amino acid residues with an O-linked carbohydrate chain that is purified from Chinese hamster ovary cells. It has a specific activity of approximately 3×10^8 colonies/10^5 nonadherent bone marrow cells per milligram of protein [12]. The G-CSF used in this study was supplied as a white, freeze-dried powder, and the vials (250 μg/vial) were stored at 4° C prior to use. In our previous dose-finding study using G-CSF in patients receiving the MVP regimen [14], s. c. injections of G-CSF at a daily dose of ≥2 μg/kg on days 2–15 after the initiation of chemotherapy were thought to be effective. Therefore, G-CSF was given s. c. at a daily dose of 2 μg/kg in the present trial. The G-CSF solution was prepared by diluting the daily dose with sterile water to yield a final volume of 1 ml. G-CSF was injected s. c. in the upper arm at 8:00 a. m. daily from day 2 to day 21 of each MVP cycle.

Data collection was confined to the first two cycles of chemotherapy. Statistical analyses were performed using the chi-square test and Student's *t*-test. Fisher's exact test was used if fewer than five patients were expected to fall within one of the categories analyzed. The absolute neutrophil count and the period of neutropenia were analyzed by Student's *t*-test for unmatched pairs (single-rank).

Results

Patients

The characteristics of patients in the two groups are shown in Table 1. The two groups did not differ in terms of sex, age, histology, and stage, although patients in the control group had a slightly poorer performance status and six patients in the G-CSF group had previously been treated with regimens containing cisplatin.

Of the 40 patients in the G-CSF group, 3 were nonevaluable for toxicity because of early death (1), protocol violation (1), and refusal of treatment (1). Another patient was not assessable for response because he exhibited no lesion that could be evaluated after the start of treatment. In all, 5 patients could not receive the second course of MVP treatment due to renal toxicity (2), gastric ulcer (1), and progressive disease (2). Of the 37 evaluable patients, 32 (84%) were capable of receiving their scheduled chemotherapy on the 22nd day of the treatment cycle. A mean of 2.7 cycles/patient were given (range, 1–5). In the control group, all patients were assessable for toxicity and response.

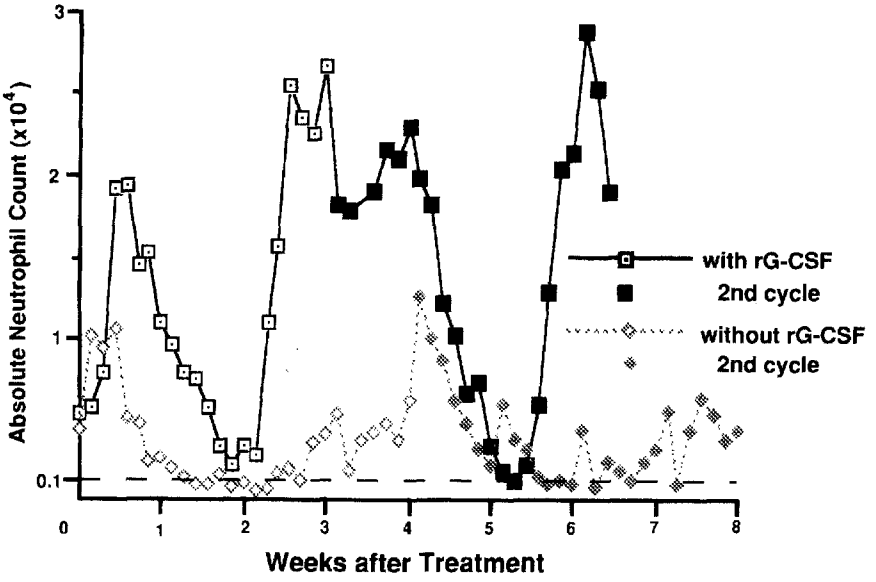

Fig. 2. Absolute neutrophil counts (/μl) obtained in patients through the 1st and 2nd cycles of MVP therapy in the presence (*with G-CSF*) and absence (*without G-CSF*) of G-CSF administration

Table 1. Patients' characteristics

	+ G-CSF	− G-CSF[a]	X^2
Patients entered	40	38	
Evaluable patients	37	38	
Sex (M/F)	34/6	29/9	NS
Median age (years)	63	65	NS
Histology:			
Adenocarcinoma	21	22	
Squamous-cell carcinoma	13	14	NS
Large-cell carcinoma	6	2	
Stage:			
IIIA	11	15	
IIIB	10	7	NS
IV	19	16	
ECOG PS:			
0	7	3	
1	27	19	$P<0.01$
2	6	16	
Prior treatment:			
Yes/no	6/34	0/38	$P<0.05$
Absolute neutrophil count before therapy	5224±3619	4644±2127	NS

[a] Patients treated with the conventional 28-day MVP regimen
NS, not significant

Neutrophil profiles

The mean absolute neutrophil counts (ANC) obtained during the first and second cycles in the control and G-CSF groups are shown in Fig. 2. Patients in the control group experienced prolonged periods of neutropenia. In contrast, the patients given G-CSF exhibited a prominent increase in ANC on the 1st day after the initiation of G-CSF treatment followed by a moderate nadir and experienced a substantially shorter period of neutropenia and a more rapid recovery as compared with those observed in the control group. These indicators of neutropenia are compared according to treatment group in Table 2. Significant differences were found between the two groups in terms of mean ANC nadirs (2666/μl in the first cycle and 1396/μl in the second cycle for the G-CSF group vs 416/μl in the first cycle and 685/μl in the second cycle for the controls ($P<0.0001$) and the mean duration of neutropenia (≤ 1000/μl; 1.0 day in the first cycle and 1.7 days in the second for the G-CSF group vs 8.0 days in the first cycle and 6.9 days in the second for the controls; $P<0.0001$). As a result, patients in the G-CSF group were capable of receiving MVP treatment on day 22 of the second cycle.

Fever with neutropenia

The incidence of febrile episodes ($\geq 38^{\circ}$C) with accompanying neutropenia during the first and second cycles of treatment was lower in the G-CSF group (Table 2). In the control group, 20 of 38 patients (53%) experienced neutropenia with fever during the first and second courses (18 in the first cycle and 7 in the second) as compared with 5 of 37 patients (14%) in the G-CSF group (5 in the first cycle and 1 in the second; $P<0.01$).

Bone marrow

Bone marrow aspirates were taken from ten patients before treatment and on the last day of the first course of G-CSF (Fig. 3). The percentages of band neutrophils and myelocytes showed a significant increase after G-CSF administration as compared with those noted prior to G-CSF treatment ($P<0.05$).

Tumor response and side effects

Tumor response was evaluable in 39 patients in the G-CSF group and in 38 in the control group (Table 3). Responses were observed in 17 patients (44%) in the G-CSF group

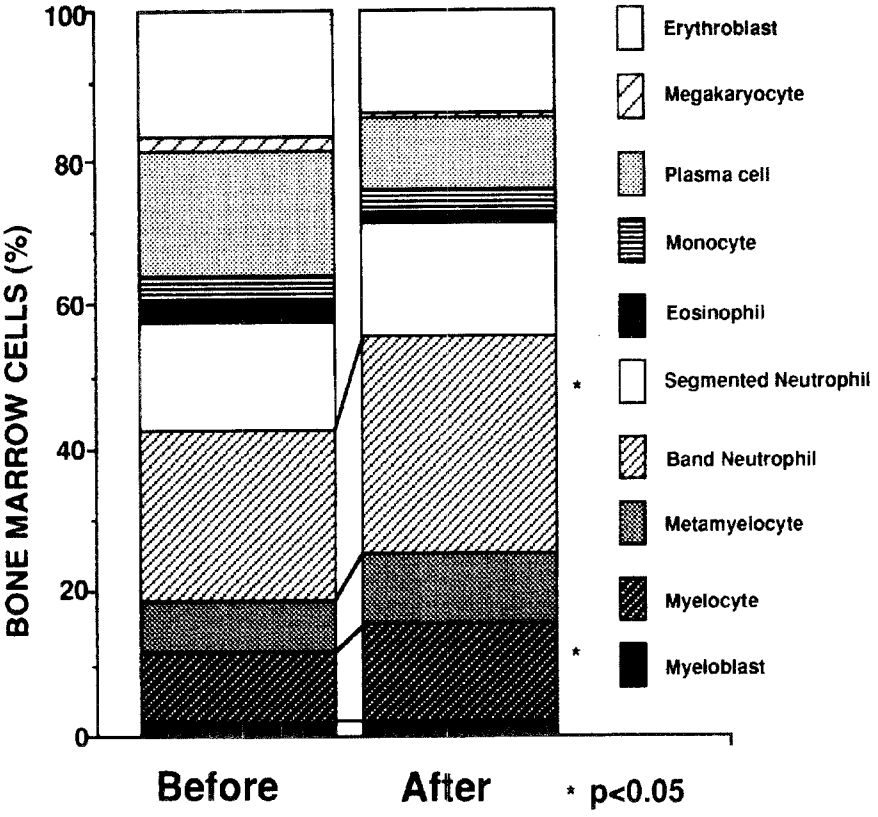

Fig. 3. Bone-marrow-cell counts obtained in 10 patients before and after G-CSF administration

Table 2. Indicators of neutropenia[a]

Indicator	+ G-CSF ($n = 37$)	− G-CSF ($n = 38$)	P value
Mean neutrophil nadir:			
1st cycle	2666 ±2374/μl	416 ± 439/μl	$P < 0.0001$
2nd cycle	1396 ±1793/μl	685 ±1096/μl	$P < 0.05$
Mean duration of neutropenia:			
1st cycle	1.0 ± 1.6 days	8.0 ± 5.9 days	$P < 0.0001$
2nd cycle	1.7 ± 1.9 days	6.9 ± 4.5 days	$P < 0.0001$
Mean duration of recovery from neutropenia:			
1st cycle	0.7 ± 1.1 days	6.3 ± 5.1 days	$P < 0.0001$
2nd cycle	1.2 ± 1.4 days	5.2 ± 4.3 days	$P < 0.0001$
Episodes of neutropenia with fever:			
1st cycle	5	18	
2nd cycle	1	7	
Total course	5 (14%)	20 (53%)	$P < 0.01$

[a] Defined as a neutrophil count of ≤1000/μl

Table 3. Tumor response to MVP in the presence and absence of G-CSF

Response	+ G-CSF ($n = 39$)	− G-CSF ($n = 38$)
Complete response	1 (3%)	1 (3%)
Partial response	16 (41%)	15 (39%)
No change	18	15
Progressive disease	4	7

(1 complete response and 16 partial responses) and in 16 patients (42%) in the control group (1 complete response and 15 partial responses). None of the six patients in the G-CSF group who had received previous chemotherapy responded.

Although no major side effect was observed in the patients receiving G-CSF, one patient showed a slight elevation in alkaline phosphatase and two patients exhibited a modest elevation in lactate dehydrogenase (LDH); these increases may have been related to the patients' ANC. No toxicity associated with mitomycin C (including pulmonary toxicity) was documented in either the G-CSF group or the historical control goup.

Discussion

In the present trial it was noteworthy that neutropenia was less severe and lasted for shorter periods in the patients

who received MVP with G-CSF support. As a result, treatment with MVP at 21-day intervals was easily accomplished in these patients. Gabrilove et al. [8] investigated the use of G-CSF in transitional carcinoma of the urothelium and also found that the administration of G-CSF enabled patients to receive their day-14 M-VAC (methotrexate, doxorubicin, vinblastine, and cisplatin) chemotherapy on schedule as compared with less than one-third of the patients who were not given G-CSF. Considering these results, the availability of G-CSF will enable the use of more intensive chemotherapy regimens in a variety of human cancers.

Our trial also clearly demonstrated that G-CSF given to patients with NSCLC as an adjuvant to MVP treatment resulted in significant reductions in the incidence of fever with neutropenia. In their phase I/II and phase III studies in the treatment of small-cell lung cancer, respectively, Bronchud and co-workers [2] and Crawford et al. [5] noted that G-CSF reduced the degree and duration of chemotherapy-associated neutropenia as well as the overall number of days of intravenous antibiotic use and of hospitalization.

In the present trial, the major effects on the bone marrow in patients treated with G-CSF were increases in the proportions of band neutrophils and myelocytes (Fig. 2). Morstyn et al. [10] reported an apparent increase in the early myeloid cell pool in patients treated with G-CSF. Thus, the early ANC elevation would appear to have been due to the migration of neutrophils from the marginal pool and the later elevation, to the release of neutrophils from the bone marrow. This would explain the phenomenon of the biphasic response of ANC, which was noted in our study as well as in patients receiving cytotoxic drugs and G-CSF in previous trials [8].

The toxicity of G-CSF was minimal, the only side effects encountered being elevation in LDH and alkaline phosphatase, which have been noted in other reports as well [2, 6, 9, 10].

Finally, in our trial, no therapeutic benefit was obtained from the response stemming from the increased dose intensity (Table 3), although the dose intensity achieved in the G-CSF group was about 1.3-fold that attained in the control group. Further studies are needed in patients undergoing more dose-intensive therapy to address the question as to whether the benefits gained from a dose-intensive regimen might lead to improved response rates and survival among patients receiving this form of treatment.

The present study demonstrated that treatment with MVP at 21-day intervals is possible with the support of G-CSF, resulting in a significant reduction in the incidence of neutropenic fever, and that this may afford the patient with advanced NSCLC better therapeutic results. The results also suggest that further shortening of MVP treatment cycles and/or increasing of the drug doses used are plausible. In keeping with the direction suggested by the present results, our next step will be to address the usefulness of G-CSF in terms of tumor response, progression-free survival, and survival duration.

Acknowledgements. We thank Mr. Y. Yoshida and Mr. A. Yamao of the Chugai Pharmaceutical Company for their assistance in the collection of data and are grateful to Mr. B. Hammond for checking the mechanics of this paper.

References

1. Bodey GP, Buckley M, Sathe YS, Freireich EJ (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64: 328
2. Bronchud MH, Scarffee JH, Thatcher N, Crowther D, Souda LM, Alton NK, 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
3. Bunn PA Jr (1989) The expanding role of cisplatin in the treatment of non-small cell lung cancer. Semin Oncol 16 [Suppl 6] 10
4. Coldman AJ, Goldie JH (1987) Impact of dose-intense chemotherapy on the development of permanent drug resistance. Semin Oncol 14 [Suppl 4]: 29
5. Crawford J, Ozer H, Stoller R, Jahnson D, Lyman G, Tabbara I, Kris M, Grous J, Picozzi V, Rausch G, Smith R, Gradishar W, Yahanda A, Vincent M, Stewart 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
6. Eguchi K, Sasaki S, Tamura T, Sasaki Y, Shinkai T, Yamada K, Soejima Y, Fukuda M, Fujihara Y, Kunitou H, Tobinai K, Ohtsu T, Suemasu K, Takaku F, Saijo N (1989) Dose escalation study of recombinant human granulocyte colony-stimulating factor (KRN 8601) in patients with advanced malignancy. Cancer Res 49: 5221
7. Fukuoka M, Masuda N, Furuse K, Negoro S, Takada M, Matui K, Takifuji N, Kudoh S, Kawahara M, Ogawara M, Kodama N, Kubota K, Yamamoto M, Kusunoki Y (1991) A randomized trial in inoperable non-small-cell lung cancer: vindesine and cisplatin versus mitomycin, vindesine, and cisplatin versus etoposide and cisplatin alternating with vindesine and mitomycin. J Clin Oncol 9: 606
8. 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, Souda L (1988) Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. N Engl J Med 318: 1414
9. Morstyn G, Souza LM, Keech J, Sheridan W, Campbell L. Alton NK, Green M, Metcalf D, Fox R (1988) Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy Lancet I: 667
10. Morstyn G, Campbell L, Lieschke G, Layton JE, Maher D, O'Connor M, Green M, Sheridan W, Vincent M, Alton K, Souda L, McGrath K, Fox RM (1989) Treatment of chemotherapy-induced neutropenia by subcutaneously administered granulocyte colony-stimulating factor with optimization of dose and duration of therapy. J Clin Oncol 7: 1554
11. Nagata S, Tsuchiya M, Asano S, Kaziro Y, Yamazaki T, Yamamoto O, Hirata Y, Kubota N, Oheda M, Nomura H, Ono M (1986) Molecular cloning and expression of cDNA for human granulocyte colony-stimulating factor. Nature 319: 415
12. Nomura H, Imazeki I, Oheda M, Kubota N, Tamura M, Ono M, Ueyama Y, Asano S (1986) Purification and characterization of human granulocyte colony-stimulating factor (G-CSF). EMBO J 5: 871
13. Ono M (1991) Pharmacological effect of recombinant human granulocyte colony-stimulating factor. In: Quesenberry P. J. et al. (eds) Hematopoietic growth factors. Excerpta Medica, Tokyo, p 121
14. Ota K, Ariyoshi Y, Fukuoka M, Furuse K, Niitani H (1990) Clinical effect of recombinant human G-CSF on neutropenia induced by the chemotherapy for lung cancer. Jpn J Cancer Chemother 17: 65
15. Welte K, Bonilla MA, Gillio AP, Boone TC, Potter GK, Gabrilobe JL, Moore MAS, O'Reilly RJ, Souza LM (1987) Recombinant human granulocyte colony-stimulating factor: effects on hematopoiesis in normal and cyclophosphamide-treated primates. J Exp Med 165: 941