Eur J Cancer, Vol. 29A, No. 5, pp. 677–680, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Recombinant Human Granulocyte Colony-stimulating Factor in Patients Receiving Intensive Chemotherapy for Non-small Cell Lung Cancer

Kiyoshi Mori, Yoshikuni Saitoh and Keigo Tominaga

This study was aimed at preventing of chemotherapy-induced neutropenia and improving the therapeutic result by reducing the cycle length of cisplatin (25 mg/m²/ day, 5-day continuous infusion) and vindesine (3 mg/m², bolus, days 1 and 8) (PiV) through the use of recombinant human granulocyte colony-stimulating factor (rG-CSF) (2–5 μg/kg/day, subcutaneous, days 6–21) for non-small cell lung carcinoma (NSCLC). PiV regimen with rG-CSF was repeated every 21 days. 28 out of 33 previously untreated patients, who completed two or more cycles of PiV regimen on schedule, were evaluable for analysis. The absolute neutrophil count in the third week after chemotherapy was 8187 ± 5376/ml. It became possible to administer PiV therapy at 3-week intervals. The response rate was 74% (23/31). In conclusion, the combined administration of rG-CSF enabled shortening of administration schedule of PiV therapy and increasing the dose intensity.
Eur J Cancer, Vol. 29A, No. 5, pp. 677–680, 1993.

INTRODUCTION

NO STANDARD chemotherapeutic regimen has been established for the treatment of advanced non-small cell lung cancer (NSCLC). At present, cisplatin (CDDP) is the most effective active agent for chemotherapy of NSCLC, and chemotherapy combining two or three agents one of which is CDDP is gaining widespread acceptance. In our institute, we employ combination chemotherapy (PiV therapy) consisting of 5-day continuous infusion (CI) of CDDP and vindesine (VDS) as treatment for NSCLC. In the treatment of 30 inpatients with NSCLC who had not been treated previously, a response rate of 50% (15/30) was obtained [1]. However, although PiV therapy achieves higher response rate than CDDP (CI) alone, it shows marked haemotoxicity.

In particular, leukopenia (< 3000/ml) has been seen to develop in 90% of patients receiving this regimen and is therefore a dose-limiting factor. Due to this problem, 4-week-cycle PiV therapy could not be performed as planned in 6 of the 30 patients in the above study [1]. In recent years, as a result of development of recombinant human granulocyte colony-stimulating factor (rG-CSF), it has become possible to alleviate the decrease in the leucocyte count due to chemotherapy [3–8]. We studied whether combined use of rG-CSF can (a) prevent the decrease in the leucocyte count caused by PiV therapy, (b) shorten the therapeutic cycle of PiV therapy by promoting recovery of neutrophils and (c) lead to the dose intensity of PiV therapy.

PATIENTS AND METHODS

Subjects

The subjects of this study were hospitalised patients who were diagnosed as having non-small cell lung cancer on the basis of the histological or cytological diagnosis and who satisfied the following criteria. (i) The lesion is of a measurable size, (ii) 75-year-old or less and performance status (PS) of 0–3, (iii) no prior therapy, (iv) well-retained function of the principal organs (v) normal bone marrow function (WBC ≥ 4000/ml, neutrophil ≥ 2000/ml, platelet ≥ 10×10^4/ml³. Hb ≥ 10 g/dl), (vi) no apparent infections, (vii) no apparent bone marrow metastasis, (viii) no abnormal reactions to skin test to rG-CSF, (ix) informed consent available.

Pretreatment evaluation included a medical history, physical examination, complete blood count (CBC), determination of urinary creatinine clearance, relevant laboratory tests, a chest X-ray, an electrocardiogram (ECG), complete urine analysis, and a bone marrow examination. All patients underwent bronchofibroscopy, a radionuclide bone scan, computerised tomography (CT) scan of the brain and thorax, and an abdominal ultrasound examination or CT scan. Physical examinations and chest X-rays were obtained weekly. CBC, biochemical tests and serum electrolyte determinations were performed two or three times per week. A chest CT scan and a determination of creatinine clearance were done before each course of cisplatin and vindesine. Staging was according to the 4th edition of the UICC TNM classification.

Patients were evaluated for response after completion of two cycles. Complete response (CR) was defined as the complete disappearance of all known disease as indicated by examinations done at least 4 weeks apart. Partial response (PR) was defined as a reduction of > 50% in the tumour area (determined from the product of the two longest perpendicular tumour diameters, summed over all measurable lesions) over > 4 weeks, without the appearance of new lesions. Stable disease (SD) was defined as either a reduction of < 50% or an increase of < 25% in the tumour area, without the occurrence of new lesions, over > 4 weeks. Progressive disease (PD) was defined as an increase of > 25% in the tumour area or the appearance of new lesions.

The toxicity criteria recommended by the WHO were used. Survival curves from day 1 of treatment until death were generated by the method of Kaplan and Meier.

rG-CSF for injection

The recombinant human G-CSF preparation for injection used in this study was a product of Chugai Pharmaceutical Co.,

Correspondence to K. Mori.
The authors are at the Department of Thoracic Diseases, Tochigi Cancer Center, 4-9-13, Yonan, Utsunomiya-shi, Tochigi-ken, Japan.
Revised 14 Sep. 1992; accepted 25 Sep. 1992.

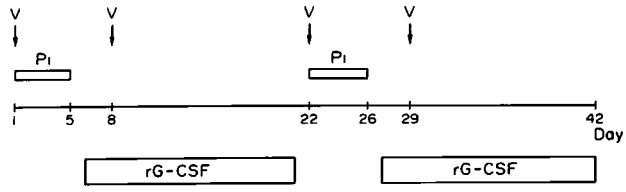

Fig. 1. Treatment regimen. Pi: cisplatin (25 mg/m²/day, continuous infusion); V: vindesine (3 mg/m², bolus); rG-CSF: recombinant human granulocyte colony-stimulating factor (2 μg/kg/day or 5 μg/kg/day, subcutaneous).

Ltd (Japan). This preparation is a lyophilised preparation and contains 250 μg of rG-CSF per vial. Each vial was dissolved in 1 ml of distilled water.

Protocol (Fig. 1)

The anticancer drug regimen consisted of combined administration of CDDP and VDS. Twenty-five mg/m² of CDDP was given daily for 5 days by continuous intravenous infusion. One third of the daily dose was administered every 8 h dissolved in 800 ml of physiological saline [2]. Three mg/m² of vindesine was administered intravenously on days 1 and 8. It was decided to administer this regimen for at least two cycles at 21-day intervals. rG-CSF for injection was administered subcutaneously in a dose of 2 μg/kg or 5 μg/kg for, in principle, 16 days (days 6 to 21), beginning on the day after the day of completion of CDDP administration, once every day, at the same time whenever possible. Patients were randomised to receive dosage of rG-CSF (2 μg/kg or 5 μg/kg). However, if the neutrophil count increased more than 5000/ml or the white blood count increased more than 10000/ml after reaching nadir, administration was discontinued. Therapy was discontinued if the disease progressed or if the patient refused further treatment.

RESULTS

33 patients were registered. Second cycle treatment could not be performed in 1 case who died early after initiation of the study and 1 case who rejected second cycle treatment. Thus, 31 patients completed the planned regimen, and their background factors are presented in Table 1. The efficacy was evaluated in the 31 patients, while the safety was evaluated in the 33 patients. 30 patients with previously untreated advanced NSCLC who were administered PiV therapy without rG-CSF were employed as the historical control.

Table 1. Patients' characteristics

Age (years)	
Median	62
Range	39–75
Sex	
Male	25
Female	6
Performance status	
0–1	26
2–3	5
Pathology	
Adenocarcinoma	15
Squamous cell	15
Adenosquamous cell	1
Staging	
III A	10
III B	11
IV	10

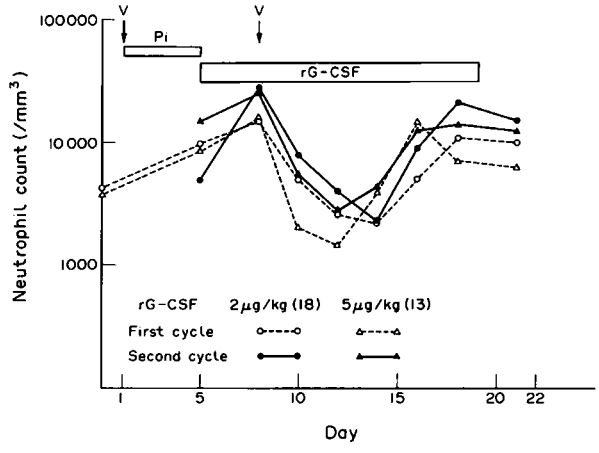

Fig. 2. Changes of mean neutrophil count in treatment. Pi: continuous infusion of cisplatin; V: vindesine; rG-CSF: recombinant human granulocyte colony-stimulating factor.

Change in neutrophil count

Among the 31 eligible patients, 18 patients were administered 2 μg/kg of rG-CSF, while 13 patients were administered 5 μg/kg. Figure 2 and Table 2 show the changes in the absolute neutrophil count (ANC) after initiation of the regimen. The nadir of ANC were 1228 (± 1508)/ml in first cycle and 2121 (± 2010)/ml in second cycle. In the 2 μg/kg rG-CSF administration group, the nadir of ANC were 1206 (± 1722)/ml and 2007 (± 2101)/ml, respectively, while it was 1424 (± 1281)/ml and 2280 (± 1949)/ml in the 5 μg/kg administration group. The nadir of ANC was recorded after about 13 days of the regimen in both cycles. The number of patients in whom the nadir of ANC reached below grade 3 (< 1000/ml) was 19 (12 in the 2 μg/kg administration group and 7 in the 5 μg/kg administration group) in first cycle and 13 (9 and 4) in second cycle.

The duration showing less than 1000/ml of the ANC was 2.95 (± 0.97) days [3.17 (± 1.03) days and 2.57 (± 0.79) days] in first cycle and 2.31 (± 1.11) days [2.00 (± 1.12) days and 3.00 (± 0.82) days] in second cycle. Patients whose ANC nadir was less than 2000/ml numbered 21 in the first cycle and 18 in the second cycle. The number of days required for the ANC to recover to 2000/ml or more was 3.19 (± 1.47) [3.07 (± 1.44) and 3.43 (± 1.62)] in first cycle and 2.39 (± 1.72) [2.09 (± 1.58)

Table 2. Neutrophil parameters—comparison of 2 μg/kg and 5 μg/kg dosages of rG-CSF

	Nadir of ANC	Duration of days with ANC < 1000/ml	Days required to recover with ANC ≥ 2000/ml
First cycle			
2 μg/kg	1206 ± 1722 (18)	3.17 ± 1.03 (12)	3.07 ± 1.44 (14)
5 μg/kg	1424 ± 1281 (13)	2.57 ± 0.79 (7)	3.43 ± 1.62 (7)
Second cycle			
2 μg/kg	2007 ± 2101 (18)	2 ± 1.12 (9)	2.09 ± 1.58 (11)
5 μg/kg	2280 ± 1949 (13)	3 ± 0.82 (4)	2.86 ± 1.95 (7)

( ): No. of patients; ANC: absolute neutrophil count; rG-CSF: recombinant human granulocyte colony-stimulating factor.

Table 3. Neutrophil parameters—comparison between rG-CSF group and control group

	Nadir of ANC	Duration of days with ANC < 1000/ml	Days required to recover with ANC ≥ 2000/ml
rG-CSF group (n = 31)	1228 ± 1508	2.95 ± 0.97 (19)	3.19 ± 1.47 (21)
Control group (n = 30)	500± 437	9.38 ± 4.31 (26)	12.4 ± 6.61 (30)
t-test	P = 0.01	P < 0.01	P < 0.01

( ): No. of patients; ANC: absolute neutrophil count;rG-CSF: recombinant human granulocyte colony-stimulating factor.

and 2.86 (± 1.95)] in the second cycle. The ANC in the third week after initiation of the regimen was 8187 (± 5376)/ml [9653 (± 6308)/ml and 6157 (± 2863)/ml] in first cycle and 13689 (± 12533)/ml [14746 (± 8339)/ml 12226 (± 17035)/ml] in second cycle. Thus, sufficient recovery had been achieved in the ANC in the third week of the regimen.

There were no differences in neutrophil parameters between the 2 μg/kg and 5 μg/kg rG-CSF administration groups.

When the 30 historical control group patients (no rG-CSF administration) was compared with the 31 rG-CSF administration group patients for neutrophil parameters in the first cycle. Significant improvement was achieved in each parameter of the nadir of ANC, duration days of ANC of less than 1000/ml and days required to recover ANC of 2000/ml or more (Table 3).

Changes in haemoglobin content and platelet count (Table 4)

The number of patients showing a haemoglobin content of 8 g/dl, i.e. below grade 3, was only one in the first cycle, while it was 8 in the second cycle. The number of patients showing a platelet count of less than 50 × 10^3/ml, i.e. below grade 3, was 4 in the first cycle and 2 in the second cycle.

Infections

Infection was diagnosed to be positive if a body temperature of at least 38°C was noted. On the basis of this criterion, infection occurred in 22 (23%) of 94 courses. The mean duration of those infections was 2.14 (± 1.06) days. The infection rate in the control group (no rG-CSF administration) was 35% (24/69 courses), which did not significantly differ from the value in the rG-CSF administration group (P = 0.11). However, the mean duration of infections in the control group was 4.42 (± 2.68) days, which was significantly (P = 0.01) longer than the value in the rG-CSF administration group.

Table 4. Haemotoxicity (n = 33)

White blood cells nadir (/ml)	
3900–3000	1
2900–2000	3
1900–1000	10
< 1000	7
Haemoglobin nadir (g/dl)	
10.9–9.5	10
9.4–8.0	5
7.9–6.0	8
Platelet nadir (× 10^3/μl)	
99–70	10
69–50	2
49–30	5

State of performance of protocol

Second cycle was able to be started as scheduled, i.e. within 3 weeks after completion of first cycle, in 28 of the 31 eligible patients. In the remaining 3 patients, the second cycle could not be started within 3 weeks after completion of the first cycle due to general malaise. However, there were no patients in which the second cycle could not be administered due to a decrease in the neutrophil count or in which the chemotherapeutic regimen had to be changed.

Response rate and survival

In the 31 eligible patients, the response to the regimen was complete response (CR) in 1 patient, partial response (PR) in 22 patients, no change (NC) in 5 patients and progressive disease (PD) in 3 patients, the response rate was thus 74%. Currently, 6 patients are alive, and the median survival time is 44 weeks.

Non-haematological side effects

General malaise was seen in 82%, vomiting in 27%, hair loss in 48% and peripheral neuropathy in 39%.

There were no side effects thought to have been due to rG-CSF. As abnormal laboratory test findings, transient increases in LDH and Cr were noted in 7 and 2 cases, respectively.

Treatment after completion of study

The same regimen was continued for a total of four cycles in 13 patients and three cycles in 3 patients. Of those patients, 12 underwent radiotherapy after chemotherapy. After completion of the two cycles as scheduled, 7 underwent radiotherapy, while 6 underwent surgical operation.

DISCUSSION

In our institute, we conducted a phase II study, consisting of 5-day continuous infusion of CDDP alone in the treatment of advanced NSCLC. A high response rate of 40% was obtained [2]. The PiV therapy was given to the patients that failed to respond to CDDP (CI) alone, and some of these responded [1, 2]. Accordingly, we then performed PiV therapy, consisting of administration of CDDP (CI) and VDS, in the treatment of NSCLC and obtained a good result of 50% in terms of the response rate [1]. However, the PiV therapy also resulted in marked haemotoxicity. Leukopenia was a particularly dose-limiting factor, and thus it was difficult to perform PiV therapy as scheduled. In combination therapy using more than one anticancer agent, its haemotoxicity, particularly leukopenia, is a principal limiting factor. Due to development of leukopenia, the planned chemotherapy is often obliged to be postponed, or the dose of the anticancer agents must be reduced, or the regimen itself must be discontinued. Moreover, leukopenia due to chemotherapy may induce infections, and this can be fatal to the patient. In order to perform cancer chemotherapy as scheduled, and safely, as well as enhancing the efficacy of the cancer chemotherapy, it is important to overcome the problem of leukopenia.

On the other hand, in recent years, studies on dose intensity have been made in relation to cancer chemotherapy. However, many of current anticancer agents cause severe neutropenia as a side effect, and thus it is difficult to achieve desired dose intensity. In recent years, it has become possible to produce granulocyte colony-stimulating factor in large amount [8, 9],

and this has lead to energetic clinical studies on neutropenia in association with cancer chemotherapy [3–8]. Takada *et al.* [7] performed dose intensity chemotherapy for lung cancer. They reported that it was possible to administer 3-week-interval cycle therapy of MVP (mitomycin, vindesine and cisplatin) as treatment of NSCLC by concomitantly administering rG-CSF, and, as a result, dose intensity was able to be increased. In our institution, we administered 4-week-cycle PiV therapy in the treatment of NSCLC and obtained a response rate of 50% (15/30). However, due to development of leukopenia, the therapy could not be completed as scheduled in 6 of 30 patients [1]. The planned dosage was 31.3 mg/m^2/week for CDDP and 1.5 mg/m^2/week for VDS, but the actual dosages were 27.5 mg/m^2/week and 1.16 mg/m^2/week, and the delivered dose intensity (DDI) was 0.88 and 0.77, respectively. As can be expected, VDS whose haemotoxicity is higher than CDDP resulted in a smaller DDI. In the present study, 3-week-cycle PiV therapy was able to be administered to 28 of 31 patients by employing concomitant administration of rG-CSF. Actual dosage was 40.4 mg/m^2/week for CDDP and 1.94 mg/m^2/week for VDS for the same DDI of 1.29. Thus, the dose intensity could be increased.

The response rate was 74% (23/31) in the rG-CSF group and 50% (15/30) in the control group (no rG-CSF administration), but the difference was not significant ($P = 0.051$). The median survival time was 44 weeks in the rG-CSF group and 39 weeks in the control group, indicating no difference. Non-haematological side effects did not differ between the two groups, but malaise was complained of by most patients of either groups, that is, 82% (27/33) of the rG-CSF group patients and 97% (29/30) of the control group patients. However, this side effect disappeared in most patients within the third week of the regimen.

Neutrophil parameters were compared between 30 control patients who had been treated with conventional 4 week interval PiV therapy without rG-CSF [1] and the patient group in the present study. The nadir of ANC, the duration showing less than 1000/ml of ANC and the number of days required for ANC to recover to 2000/ml or more were significantly ($P \leq 0.01$) better in the patient group in which rG-CSF had been administered. Thus, this study demonstrated that rG-CSF is highly effective for treatment of neutropenia caused by cancer chemotherapy. Moreover, the incidence of occurrence of infections was 23% (22/94) in the rG-CSF group and 35% (24/69) in the control group ($P = 0.11$). The mean duration of days with infections was 2.14 ($\pm$ 1.06) and 4.42 ($\pm$ 2.68), respectively, indicating a significantly ($P = 0.01$) shorter value in the rG-CSF group.

There were no significant differences in the neutrophil parameters between the 2 μg/kg and 5 μg/kg rG-CSF administration subgroups. Thus, 2 μg/kg is thought to be sufficient as the dose of rG-CSF in PiV therapy.

As described above, concomitant administration of rG-CSF prevented the decrease in the neutrophil count due to PiV therapy and promoted the recovery of the neutrophil count. As a result, it became possible to administer PiV therapy at 3-week intervals, thereby achieving a high response rate. In addition, administration rG-CSF enabled shortening of administation schedule of chemotherapy and increasing the dose intensity [7]. Currently, we are studying whether it is possible to improve therapeutic results, such as the high response rate and prolonged survival in unresectable NSCLC patients, by increasing the dose intensity in PiV therapy by concomitant administration of rG-CSF.

1. Mori K, Saitou Y, Tominaga K. Phase II study of cisplatin continuous infusion plus vindesine in the treatment of non-small cell lung cancer. *Am J Clin Oncol* 1992, **15**, 344–347.
2. Saitou Y, Mori K, Yokoi K, Tominaga K, Miyazawa N. Phase II study of 5-day continuous infusion of *cis*-diamminedichloroplatinum (II) in the treatment of non-small cell lung cancer. *Cancer Chemother Pharmacol* 1990, **26**, 389–392.
3. Eguchi K, Sasaki S, Saijo N, *et al.* Dose escalation study of recombinant human granulocyte-colony-stimulating factor (KRN8601) in patients with advanced malignancy. *Cancer Res* 1989, **49**, 5221–5224.
4. Bronchud MH, Scarffe JH, Thatcher N, *et al.* Phase I/II study of recombinant human granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for small cell lung cancer. *Br J Cancer* 1987, **56**, 809–813.
5. Morstyn G, Campbell L, Souza LM, *et al.* Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy. *Lancet* 1988, **26**, 667–671.
6. Gabrilove JL, Jakubowski A, Scher H, *et al.* 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* 1988, **318**, 1414–1422.
7. Takada M, Fukuoka M, Furse K, Ariyoshi Y, Niitani H, Ota K. Recombinant human G-CSF (rG-CSF) in patients with non-small cell lung cancer (NSCLC) treated with combination chemotherapy (CT) of mitomycin, vindesine and cisplatin (MVP). *Proc ASCO* 1990, **9**, P224 (Abstract).
8. Neidhart J, Mangalik A, Kohler W, *et al.* Granulocyte colony-stimulating factor stimulates recovery of granulocytes in patients receiving dose-intensive chemotherapy without bone marow transplantations. *J Clin Oncol* 1989, **7**, 1685–1692.
9. Nagata S, Tsuchiya M, Asano S, *et al.* Molecular cloning and expression of cDNA for human granulocyte colony-stimulating factor. *Nature* 1986, **319**, 415–417.