Cancer Chemother Pharmacol (1996) 38: 9–12

ORIGINAL ARTICLE

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Optimal schedule for administering granulocyte colony-stimulating factor in chemotherapy-induced neutropenia in non-small-cell lung cancer

Received: 13 January 1995 / Accepted: 11 August 1995

Abstract A prospective randomized study was conducted to determine the optimal schedule of rhG-CSF (recombinant human granulocyte colony-stimulating factor). A group of 33 lung cancer patients treated with MVP therapy (mitomycin, vindesine, and cisplatin) were randomly assigned to three groups: an early prophylaxis group in which rhG-CSF was initiated on day 2 of the MVP cycle; a late prophylaxis group in which rhG-CSF was initiated on day 8; and a therapeutic group in which rhG-CFS was initiated after the onset of neutropenia. Ten patients who had received MVP therapy without rhG-CSF were also analyzed as a no-support group. The incidence of neutropenia was 80% (16/20 courses) in the early prophylaxis group, 44% (8/18) in the late prophylaxis group, 94% (17/18) in the therapeutic group, and 94% (16/17) in the no-support group. The incidence of neutropenia in the late prophylaxis group was less than in the early prophylaxis group ($P < 0.05$), the therapeutic group ($P < 0.01$), and the no-support group ($P < 0.01$). The late prophylactic rhG-CSF schedule was therefore more effective in countering neutropenia than either the early prophylactic or therapeutic schedule.

Key words Hematopoietic growth factor · Lung cancer · Chemotherapy · Neutropenia

Introduction

Recombinant human granulocyte colony-stimulating factor (rhG-CSF) induces proliferation and differentiation of neutrophil lineage cells, and potentially reduces the severity of neutropenia and infections. Although rhG-CSF is used in various clinical applications, the optimal schedule and dose remain unresolved [10, 11, 14]. We conducted a prospective randomized study to evaluate the effectiveness of three different schedules of rhG-CSF administration in countering neutropenia following chemotherapy for non-small-cell lung cancer.

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Materials and methods

Patient selection

This study was conducted in accordance with institutional ethical standards. The patient criteria for eligibility for entry were as follows: histologically or cytologically confirmed non-small-cell lung cancer according to the typing criteria of the World Health Organization; age below 75 years; Eastern Cooperative Oncology Group performance status of 2 or better; absence of both brain and bone marrow metastases; adequate bone marrow function with neutrophil count $>2000/\mu l$, platelet count $>100\,000/\mu l$, and hemoglobin level >10 g/dl; normal hepatic and renal functions; and the provision of informed consent. Patients who had received prior chemotherapy or radiotherapy were also eligible, if the last course had been completed more than 4 weeks before entry. Computed tomography and bone scintigraphy were performed to determine the cancer stage according to the criteria of International Union Against Cancer. This procedure resulted in the selection of 33 patients.

Treatment schedule

Patients received MVP therapy (mitomycin C 8 mg/m^2 on day 1, vindesine 3 mg/m^2 on days 1 and 8, cisplatin 80 mg/m^2 on day 1) for one or two 28-day cycles [17]. The therapy was discontinued if the disease progressed or if the patient refused further treatment. The rhG-CSF (Lenograstim; Chugai Pharmaceutical Company, Tokyo, Japan) was administered subcutaneously by bolus injection at a dose of 2 μg/kg on the scheduled days. Lenograstim is glycosylated rhG-CSF purified from Chinese hamster ovary cells [15], and the dose of 2 μg/kg is routinely employed in Japan [13, 17].

The 33 patients were randomly assigned to three groups, which differed in rhG-CSF schedule: an early prophylaxis group in which rhG-CSF administration was started on day 2 of the MVP cycle; a late prophylaxis group in which rhG-CSF administration was started on day 8 of the MVP cycle, and a therapeutic group in which rhG-CSF administration was started on the first day of neutropenia. Neutropenia

Table 1 Patient characteristics

	Early prophylaxis group	Late prophylaxis group	Therapeutic group	No-support group
No. of patients	11	11	11	10
No. of courses	20	18	18	17
Age (years)				
Median	65	66	70	67
[25%, 75%]	[63, 69]	[62, 68]	[62, 73]	[63, 71]
Gender				
Male	7	9	5	8
Female	4	2	6	2
Performance status				
0–1	10	9	11	9
2	1	2	1	1
Stage				
I-III	4	4	6	6
IV	7	7	5	4
Histology				
Adenocarcinoma	8	8	8	8
Squamous cell	3	2	3	2
Large-cell	0	1	0	0
Prior therapy				
Present	0	0	0	1
Absent	11	11	11	9

was defined as a neutrophil count of $<1000/\mu l$. The administration of rhG-CSF was discontinued either when the neutrophil count exceeded $5000/\mu l$ after nadir or when the agent had been administered for 14 days. Although vindesine and rhG-CSF were concurrently administered on day 8 in the early and late prophylaxis groups, this administration of rhG-CSF was accepted in previous studies of the MVP and cisplatin/vindesine regimens [13, 17]. Ten patients who had received the MVP regimen without rhG-CSF were studied as a no-support group.

Complete blood cell and differential counts were performed three times per week. The patients with febrile neutropenia (a body temperature $\geq 37.5\,^{\circ}C$ and neutrophil count $<1000/\mu l$) were treated empirically with antibiotics.

Statistical analysis

The data for all four groups were first evaluated using the Kruskal-Wallis test or the Chi-squared test. If the results of either test were found to be significant, the data were compared using the Scheffe test. A two-tailed $P<0.05$ was considered to be significant. All statistical analyses were conducted using FISHER software (Medical Computer Laboratory, Tokyo University Faculty of Medicine, Japan) [9].

Results

The patient characteristics for each group are shown in Table 1. A few courses of MVP in each rhG-CSF group were not assessable due mainly to the progression of disease. No significant differences among the groups in patient characteristics were identified.

The median durations of rhG-CSF therapy were 14 days in the early prophylaxis group, 11 days in the late prophylaxis group, and 7 days in the therapeutic group. The duration of rhG-CSF therapy in the late prophylaxis group was shorter than that in the early prophylaxis group ($P<0.05$), and longer than that in the therapeutic group ($P<0.01$).

Figure 1 shows the median neutrophil count plotted on a log scale during the first and second cycles in each group. In the early prophylaxis group, the neutrophil count increased immediately after the rhG-CSF administration, and then decreased in spite of continuation of administration. The nadir was observed on day 12 followed by a rapid recovery. In the late prophylaxis group, a biphasic response was also observed, but the amplitude was minimal. In the therapeutic group, rapid recovery from neutropenia was seen after the nadir. In each group, the neutrophil count curve in the first cycle was similar to that in the second.

Table 2 shows the neutropenia parameters during all cycles in each group. The late prophylaxis group had a

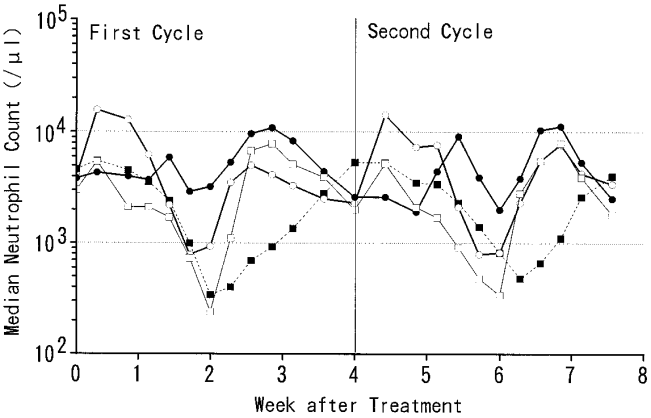

Fig. 1 Median neutrophil counts during the first and the second cycles according to the rhG-CSF schedules (○ early prophylaxis group, ● late prophylaxis group, □ therapeutic group, ■ no-support group)

Table 2 The neutropenia parameters according to the rhG-CSF schedule. Neutropenia was defined as a neutrophil count $<1000/\mu l$, and fever as a body temperature ≥ 37.5 °C

	Early prophylaxis group	Late prophylaxis group	Therapeutic group	No-support group
No. of courses	20	18	18	17
Incidence of neutropenia	16 (80%)	8 (44%)*	17 (94%)	16 (94%)
Duration of neutropenia (days)[a]	3 [2, 4]†	0 [0, 4]‡	5 [4, 6]	8 [5, 10]
Incidence of febrile neutropenia	4 (20%)	1 (6%)	6 (33%)	4 (24%)

[a] The values are medians [25%, 75%]
* $P<0.01$ compared to the therapeutic and no-support groups, and $P<0.05$ compared to the early prophylaxis group by the Scheffe test
† $P<0.01$ compared to the no-support group by the Scheffe test
‡ $P<0.01$ compared to the therapeutic and no-support groups by the Scheffe test

lower incidence and shorter duration of neutropenia than the therapeutic and no-support groups ($P<0.01$), and a lower incidence of neutropenia than the early prophylaxis group ($P<0.05$). Although the difference was not significant, the late prophylaxis group showed the lowest incidence of febrile neutropenia. On the other hand, the early prophylaxis group had a shorter duration, but not a lower incidence, of neutropenia, in spite of a longer duration of rhG-CSF treatment.

Discussion

The optimal schedule of rhG-CSF administration has not yet been determined. Such a schedule may be initiated before or after chemotherapy, either as prophylaxis or as therapy to counter established neutropenia or febrile neutropenia. This study showed that neutropenia was most effectively countered by the prophylactic schedule initiated on day 8 of the MVP cycle.

When rhG-CSF is initiated after chemotherapy, a double-peaked neutrophil count in the peripheral blood is usually observed. The first peak reflects the rapid release of stored mature neutrophils from the bone marrow, and the second the increased granulopoiesis in the bone marrow [1, 4, 6]. The effect of rhG-CSF on the peripheral neutrophil level results from the combination of the release and the proliferation of neutrophil lineage cells.

Prophylaxis with rhG-CSF is generally initiated 24 h after the main chemotherapy is completed, and is continued through the period of the neutrophil nadir [2, 13, 17]. The early rhG-CSF administration induces excessive release of mature neutrophils from the bone marrow, and transient exhaustion of the marrow neutrophil pool. The progenitor cells, damaged by chemotherapy, cannot compensate for the depletion, resulting in the transient and markedly low nadir [4, 11, 14]. Thereafter, the progenitor cells respond to rhG-CSF and provide the replacement neutrophils. Consequently, the early prophylaxis group did not show any reduction in the incidence of neutropenia, although the duration was shortened.

In the present study, vindesine and rhG-CSF were concurrently administered on day 8 in the early and late prophylaxis groups. The concurrent administration, however, was thought not significantly to influence the outcome of this study. Morstyn et al. have also observed that delaying the initiation of rhG-CSF until 7 days after a single dose of melphalan reduces the degree of neutropenia compared with that beginning 24 h after the chemotherapy [14]. Additionally, a preclinical study in nonhuman primates treated with rhG-CSF 1 day after a single dose of mechloroethamine showed a lower nadir compared with delayed therapy groups [11]. The delay in rhG-CSF administration results in release of neutrophils at the expected time of nadir and their subsequent proliferation. These two mechanisms together sustain the peripheral neutrophil level. Thus, in the prophylactic schedule, late initiation is more beneficial in countering neutropenia than early initiation.

The effectiveness of the therapeutic rhG-CSF schedule has not yet been clarified. Recent studies have indicated that the therapeutic rhG-CSF schedule reduces the duration of neutropenia, but shows no, or a borderline, effect in reducing fever [7, 8]. The initial neutrophil response to the therapeutic rhG-CSF schedule results from the mobilization and recovery of inherent neutrophils from the bone marrow. However, fatal septic shock usually ensues within 4 to 10 h after onset of established Gram-negative bacteremia, and treatment producing mobilization alone is insufficient [3]. The therapeutic rhG-CSF schedule is inferior to the prophylactic schedule.

The effects of cytotoxic drugs on hematopoietic progenitors are different [16], and the optimal schedule of rhG-CSF may vary with the type of chemotherapy regimen. Miles et al. have reported that rhG-CSF therapy after the ifosphamide/doxorubicin cycles is less effective than that following cisplatin/etoposide cycles [12]. Furthermore, a preclinical study has suggested that repeated rhG-CSF use during cyclic chemotherapy may damage the hematopoietic stem cells and induce peripheral cytopenia [5].

In conclusion, late rhG-CSF prophylaxis reduces neutropenia following MVP therapy more than early prophylaxis or therapeutic administration. The optimal timing of rhG-CSF, however, may depend on the type of chemother-

apy regimen. Further studies are necessary to clarify the interaction between rhG-CSF and cytotoxic drugs on granulopoiesis.

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