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Original Paper

A Single-blind, Randomised, Vehicle-controlled Dose-finding Study of Recombinant Human Granulocyte Colony-stimulating Factor (Lenograstim) in Patients Undergoing Chemotherapy for Solid Cancers and Lymphoma

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This study evaluated the effect of glycosylated recombinant human granulocyte colony-stimulating factor (rHuG-CSF; lenograstim) on neutrophil granulocyte counts and on cells of other haematopoietic lineages in 66 patients with solid cancer or lymphoma who received myelosuppressive chemotherapy. Beginning 1 day after completion of chemotherapy, patients received lenograstim (at dosages of 0.5, 2, 5 or 10 μg/kg) or vehicle subcutaneously once daily for 14 consecutive days. Compared with vehicle, lenograstim significantly accelerated neutrophil recovery after chemotherapy in a dose-dependent manner. Mean neutrophil counts recovered to $>1.0 \times 10^9$ cells/l by day 13 in the vehicle group compared with days 11, 10, 8 and 7 in the 0.5, 2, 5 and 10 μg/kg lenograstim groups, respectively. Doses of 0.5 and 2 μg/kg of lenograstim had a significant effect on the duration of neutropenia ($<1.0 \times 10^9$ cells/l), the area under the absolute neutrophil count (ANC) curve and the time to ANC nadir. The dose of 5 μg/kg additionally decreased the total area of neutropenia and gave the narrowest range of values for all neutrophil parameters, while the 10 μg/kg dose brought no added benefit. A dose–response effect of lenograstim on time to neutrophil recovery was observed both for patients who received chemotherapy on a single day ($n = 35$) and for those who received chemotherapy over several days ($n = 29$). Based on these findings, a dose of 5 μg/kg/day was chosen for further trials.

Key words: rHuG-CSF, lenograstim, granulocyte colony-stimulating factor, neutropenia, chemotherapy, solid cancer

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INTRODUCTION

MYELOSUPPRESSION IS one of the major dose-limiting toxicities associated with the administration of chemotherapy to patients with cancer. The success of these anticancer regimens is often limited by myelosuppression, which may result in severe and possibly life-threatening infections. Neutropenia is probably the most important factor contributing to an increased susceptibility to infection, the risk of infection rising considerably when the absolute neutrophil count falls below 1.0×10^9 cells/l [1].

It may be possible to counterbalance these dose limitations with specific haematopoietic growth factors which are capable of controlling the proliferation, differentiation and maturation of haematopoietic progenitor cells.

In contrast to granulocyte–macrophage colony-stimulating factor (GM-CSF), which acts on several types of progenitor cells in the myeloid line, G-CSF acts specifically on late progenitor cells influencing their development into functionally mature cells of the neutrophil lineage. The availability of G-CSF as a product of recombinant technology (rG-CSF) has permitted its clinical use in the amelioration of neutropenia of various aetiologies. Evidence indicates that intravenously or subcutaneously administered rG-CSF dose-dependently accelerates neutrophil recovery after chemotherapy, leading to a reduction in duration of the neutropenic phase [2]. Preventing neutropenia or reducing its duration and severity may result in a significant decrease in the mortality and morbidity associated with chemotherapy.

The objectives of this study were to evaluate the efficacy and tolerability of subcutaneously administered glycosylated recombinant human granulocyte colony-stimulating factor (rHuG-CSF; lenograstim) in neutropenic patients with solid cancer or lymphoma treated with chemotherapy; the effects of a range of lenograstim dosages on neutrophil granulocyte counts and cells of other haematopoietic lineages; and the efficacy of these dosages in preventing or reducing the severity of neutropenia (defined as $<1.0 \times 10^9$ cells/l), in reducing the duration of neutropenia, and in preventing or reducing the occurrence of infections in patients after chemotherapeutic treatment.

PATIENTS AND METHODS

66 patients were enrolled from 12 centres in the U.K., Belgium and Germany. They were eligible for enrolment if they were between the ages of 18 and 75 years, and had a confirmed diagnosis of solid cancer or lymphoma without evidence of bone marrow involvement. Each patient included in the study received chemotherapy which was expected to cause a nadir absolute neutrophil count (ANC) $<1.0 \times 10^9$/l. This was based either on historical data for a particular regimen or on the patient's personal experience of neutropenia in a previous cycle using the same drug combination. Eligible patients had a life expectancy of at least 3 months, and a Karnofsky performance score of at least 50. Patients were also required to meet standard criteria for renal, hepatic, metabolic, cardiac and haematological status, and were to have no other serious illnesses. Patients with neutropenia or thrombocytopenia unrelated to chemotherapy were to be excluded. All patients gave informed consent to participate. Ethical committees at each participating centre gave their approval to the study protocol.

Drug administration

Lenograstim (Chugai Pharmaceutical Co. Ltd, Tokyo, Japan) is expressed in Chinese hamster ovary cells transfected with a vector containing G-CSF cDNA derived from a human cell line (CHU-2), which constitutively produces high levels of G-CSF.

Lenograstim was supplied as a sterile lyophilised preparation for injection, in vials each containing 33.6 mIU (263 μg) lenograstim. Vehicle was supplied in identical vials.

Patients were randomly assigned to receive vehicle or one of four lenograstim dosages: 0.5, 2, 5 or 10 μg/kg. Treatment was administered subcutaneously once daily at the same time every day for 14 consecutive days, beginning the day after the last administration of any myelotoxic drug and a maximum of 5 days after the beginning of the cycle. Patients were observed for an additional 4 days post-treatment, for a total study period of 18 days.

Administration of potentially myelotoxic drugs was not permitted after the start of lenograstim therapy, or during the 4-day post-treatment period. Immunomodulating agents, or any other agent thought to interfere with the chemotherapeutic regimen or with lenograstim therapy was not allowed. Prophylactic antibiotic therapy was not permitted but therapeutic use of antibiotics was permitted if infection occurred.

Efficacy and safety evaluations

The primary outcome measure was ANC, measured at baseline, and at least every other day during treatment (daily during neutropenia).

The main goal of the study was to determine whether the administration of lenograstim significantly increased the production of neutrophils in the patients being studied and whether the increase was dose-related. The primary efficacy variables were the following six changes in neutrophil count: level of neutrophil count nadir after chemotherapy, time to neutrophil count nadir, total area under the neutrophil count curve, number of days that the neutrophil count was $<1.0 \times 10^9$ cells/l, number of days that the neutrophil count was $<0.5 \times 10^9$ cells/l, and area below 1.0×10^9 cells/l on the neutrophil count curve. Patients were also observed daily for signs of infection.

Measures used to evaluate safety were medical history, physical examination including vital signs, observation of the injection site, tumour status, laboratory test results and reports of adverse experiences.

Statistical analysis

In planning this study, an average minimum neutrophil count of 1.0×10^9 cells/l with a standard deviation of 0.37×10^9 cells/l in the vehicle group was assumed, based upon information from a previous G-CSF study in cancer patients receiving chemotherapy [3]. It was estimated that a sample size of 60 evaluable patients (12 in each treatment group) would be required to detect a 40% difference in minimum neutrophil count between the vehicle group and any of the active treatment groups, with 80% power and a one-sided α-level of 0.05 [4].

Differences in demographic and baseline disease characteristics between treatment groups were assessed using a one-way analysis of variance (ANOVA) [5] for continuous variables (e.g. age) and the chi-squared test [6] for categorical data (e.g. sex).

The primary efficacy analysis and incidence of infection were based on results obtained during the 14-day treatment period plus 4 days post-treatment. Two approaches to the analysis were taken because of the non-normality of the distribution of data. Firstly, non-parametric Kruskal–Wallis tests were applied to each of the primary efficacy variables and pairwise treatment comparisons were made using Wilcoxon two-sample tests. In order to provide a comparison with the non-parametric analysis,

efficacy parameters were also analysed by a parametric one-way ANOVA, with pairwise treatment comparisons made using Fisher's least significant difference (LSD) procedure. The presence of a dose–response relationship was assessed using linear regression analysis. Differences in rates of infection between treatment groups were analysed using the chi-squared test. A P value of ≤ 0.05 was regarded as statistically significant. Calculations were performed using the Statistical Analysis System (SAS) Version 5.18, software package [7].

RESULTS

Between August 1989 and January 1991, 66 outpatients (44 females and 22 males) with solid cancer or lymphoma were entered into the study. All patients had undergone chemotherapy treatment and were likely to experience neutropenia. Patients were randomly assigned to receive vehicle (n = 13) or lenograstim 0.5, 2, 5 or 10 μg/kg (n = 14, 12, 15 and 12, respectively). Study medication was administered once daily by subcutaneous injection for 14 days, beginning the day after completion of a myelotoxic anticancer therapeutic regimen.

Treatment groups were similar with respect to age, sex, race, primary diagnosis and baseline performance status (Table 1). However, the time from primary diagnosis was significantly longer in the vehicle group than in any of the lenograstim treatment groups (P = 0.035). In addition, significantly more patients in the lenograstim 10 (50%) and 5 (53%) μg/kg groups had received previous radiotherapy compared with patients in the other three treatment groups (P = 0.011).

The types and numbers of cycles of chemotherapy received by each treatment group prior to the study medication were comparable. Overall, 18 patients (27% of the study population) received epirubicin alone and 48 (73%) received combination chemotherapy. 51 patients (77%) qualified for entry into the study due to previous chemotherapy-related neutropenia, and the remaining 15 (23%) had no qualifying cycle but were enrolled on the basis of historical data indicating that the regimens used in this study would cause neutropenia. In 10 of these 15 cases, epirubicin 120 mg/m^2 was given as a single agent.

Of the 66 patients enrolled, 55 (83%) completed the 14-day treatment regimen, and 53 (80%) completed the 18-day study

Table 1. Demographic and baseline disease characteristics (all enrolled patients)

Characteristic	All patients	Lenograstim (μg/kg/day)			
		Vehicle (n = 13)	0.5 (n = 14)	2 (n = 12)	5 (n = 15)	10 (n = 12)
Age (years)						
Mean		52.2	54.7	51.2	54.0	51.1
S.D.		9.3	11.8	13.9	13.1	12.3
Range		36–65	23–72	29–72	26–73	33–66
Sex, n (%)						
Male	22	4 (31)	5 (36)	3 (25)	5 (33)	5 (42)
Female	44	9 (69)	9 (64)	9 (75)	10 (67)	7 (58)
Primary diagnosis, n (%)						
Mammary carcinoma	34	7 (54)	8 (57)	7 (58)	6 (40)	6 (50)
Small cell lung cancer	16	3 (23)	4 (29)	2 (17)	4 (27)	3 (25)
Non-Hodgkin's lymphoma	6	1 (8)	0 (0)	1 (8)	2 (13)	2 (17)
Hodgkin's lymphoma	5	1 (8)	1 (7)	1 (8)	1 (7)	1 (8)
Non-small cell lung cancer	2	1 (8)	0 (0)	0 (0)	1 (7)	0 (0)
Ovarian cancer	2	0 (0)	1 (7)	0 (0)	1 (7)	0 (0)
Gastric cancer	1	0 (0)	0 (0)	1 (8)	0 (0)	0 (0)
Time from primary diagnosis (months)						
Mean		59.7*	21.5	27	12.5	36.6
S.D.		64.1	22.1	34.3	8.7	43.1
Range		1.5–198	2–69	1–123	2–26	1–106
Karnofsky performance status, n (%)						
100	5	1 (8)	1 (7)	0 (0)	2 (13)	1 (8)
80 or 90	42	10 (77)	7 (50)	8 (67)	9 (60)	8 (67)
60 or70	19	2 (15)	6 (43)	4 (33)	4 (27)	3 (25)
Previous radiotherapy, n (%)						
No	47	12 (92)	13 (93)	9 (75)	7 (47)	6 (50)
Yes	19	1 (8)	1 (7)	3 (25)	8 (53)†	6 (50)†
Chemotherapy in this study, n (%)						
Epirubicin	18	4 (31)	4 (29)	3 (25)	3 (20)	4 (33)
Combination	48	9 (69)	10 (71)	9 (75)	12 (80)	8 (67)
Qualifying cycle, n (%)						
No	15	5 (38)	2 (14)	3 (25)	1 (7)	4 (33)
Yes	51	8 (62)	12 (86)	9 (75)	14 (93)	8 (67)

Statistical significance: * $P < 0.05$ versus active treatments (ANOVA); † $P < 0.05$ versus vehicle, 0.5 and 2 μg/kg/day (chi-square).

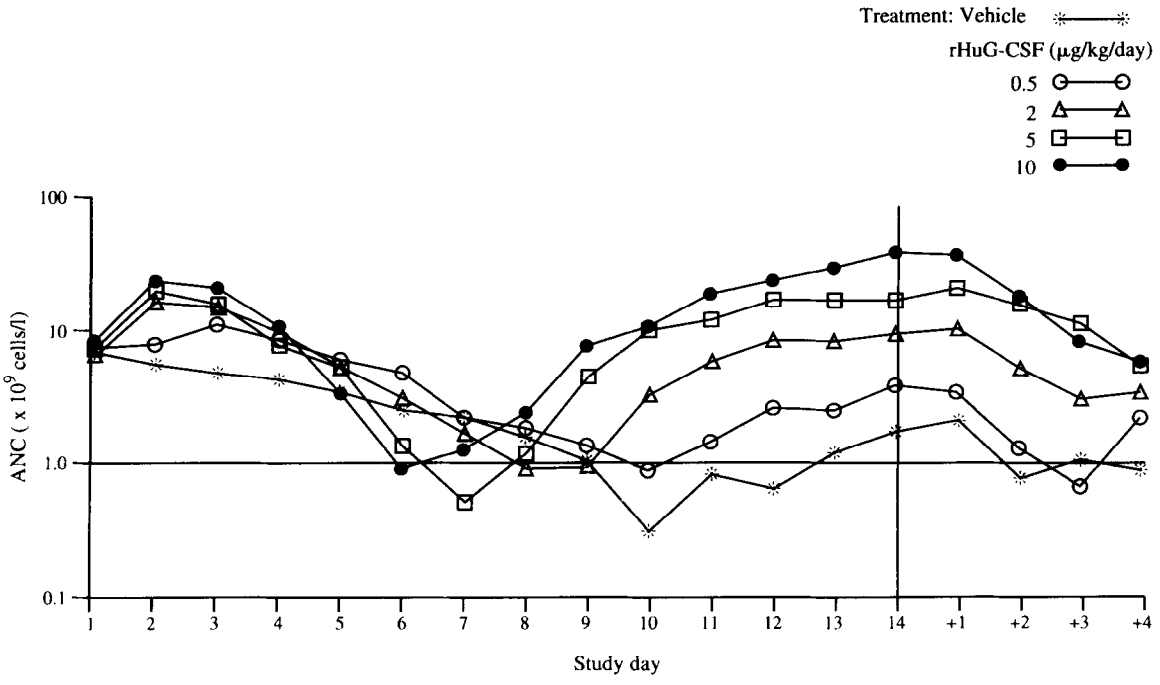

Figure 1. Mean absolute neutrophil count (ANC) in 64 evaluable patients with solid cancer or lymphoma who were treated for 14 days with lenograstim or vehicle. Plot is based on observed values only; no interpolation or estimation of missing values was applied.

period. 13 patients discontinued treatment prematurely, 9 because of an increased WBC count (>30 × 10^9 cells/l), which was a requirement of the protocol. 3 patients stopped treatment because of adverse experience(s), and 1 patient was withdrawn at the discretion of the investigator. Protocol violations consisted mainly of patients receiving lenograstim after recording excessive increases in neutrophil or WBC counts, but these were not considered to have significantly affected the results.

Neutrophil response

2 patients, 1 from the vehicle group and 1 from the lenograstim 2 μg/kg group, were excluded from the neutrophil response analysis because of incomplete neutrophil count assessments. Thus, the analysis was based on data from 64 evaluable patients. In 35 patients chemotherapy was given on a single day, while 29 patients received chemotherapy on more than 1 day. In all cases lenograstim or vehicle was commenced on the day after completion of chemotherapy.

For all 64 evaluable patients, those treated with lenograstim demonstrated a dose-related acceleration in neutrophil recovery from the day after completion of chemotherapy compared with those who received vehicle. Mean neutrophil counts recovered to >1.0 × 10^9 cells/l by day 13 in the vehicle group compared with days 11, 10, 8 and 7 in the 0.5, 2, 5 and 10 μg/kg lenograstim groups, respectively (Figure 1).

Table 2 summarises the results of the neutrophil response analysis. The median neutrophil count nadir was lower in patients treated with vehicle compared with patients who

Table 2. Summary of neutrophil response in 64 evaluable patients. Data are expressed as median values (range)

Parameter	Vehicle (n = 12)	Lenograstim (μg/kg ↓ y) 0.5 (n = 14)	2 (n = 11)	5 (n = 15)	10 (n = 12)
Neutrophil count nadir (×10^9 cells/l)	0.146 (0–1.305)	0.624 (0–1.980)	0.260 (0.010–2.442)	0.396 (0.08–9.912)	0.552 (0.042–1.476)
Days to neutrophil count nadir	12 (7–15)	10 (8–13)	8*† (7–11)	7*†‡ (5–9)	7*†‡ (5–12)
Total area under the neutrophil count curve (×10^9 cells × days/l)	29 (11–125)	81* (19–123)	130*† (45–167)	177*†‡ (80–309)	233*†‡ (80–489)
Median duration of neutropenia <1.0 × 10^9/l (days)	8.5 (1–11)	2* (0–12)	3* (0–7)	2* (0–4)	2* (0–6)
Total area of neutropenia <1.0 × 10^9/l	5 (0–9.3)	0.5 (0–9.6)	1.1 (0–5.9)	1.1* (0–3.1)	0.4* (0–1.9)

Statistical significance: * $P < 0.05$ versus vehicle; † $P < 0.05$ versus lenograstim 0.5 μg/kg; ‡ $P < 0.05$ versus lenograstim 2 μg/kg (Kruskal–Wallis test and Wilcoxon two-sample test).

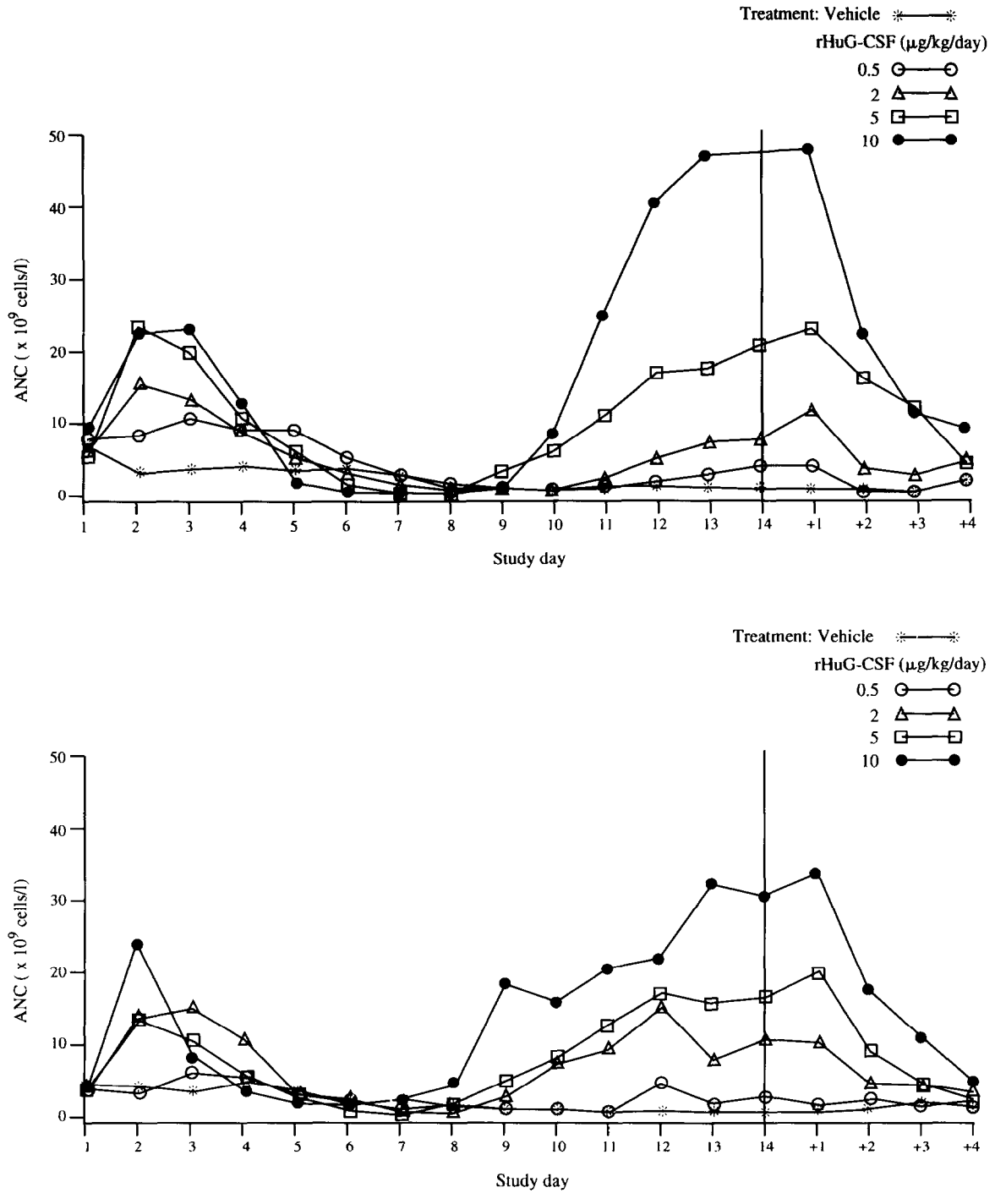

Figure 2. (a) Median absolute neutrophil count (ANC) in patients receiving chemotherapy on 1 day (n = 35). (b) Median ANC in patients receiving chemotherapy on more than 1 day (n = 29). Lenograstim was started on the day following the last chemotherapy dose for 14 days.

received lenograstim, but the differences between treatment groups were not statistically significant.

The neutrophil count nadir occurred earlier with doses of lenograstim above 2 μg/kg. The median time to neutrophil nadir was 12 and 10 days for patients in the vehicle and in the 0.5 μg/kg groups, respectively, while it was 7–8 days for patients receiving ≥2 μg/kg/day ($P < 0.05$).

The median total area under the ANC curve for the lenograstim 10 and 5 μg/kg groups was significantly higher than that for the lenograstim 2 μg/kg group, which was itself significantly higher than that for the 0.5 μg/kg group. All lenograstim groups were significantly different from vehicle ($P < 0.05$ in all cases).

The median duration of neutropenia ($<1.0 \times 10^9$ cells/l) was significantly longer in the vehicle group compared with those treated with lenograstim (8.5 versus 2–3 days; $P < 0.05$); however, there were no significant differences among the four lenograstim dosage groups. There was no statistically significant difference between treatment groups in the median duration during which the neutrophil count was $<0.5 \times 10^9$ cells/l. The total area of neutropenia below 1.0×10^9 cells/l on the

Table 3. Summary of the most frequently reported clinical adverse events, regardless of relation to study medication. Data are expressed as number of events reported. Some patients experienced more than one adverse event

Adverse events	Vehicle (n = 13)	Lenograstim (μg/kg/day) 0.5 (n = 14)	2 (n = 12)	5 (n = 15)	10 (n = 12)
Nausea	2	2	0	3	3
Infection/inflammatory disorder of the buccal cavity*	2	1	2	1	3
Insomnia	0	3	0	0	0
Myalgia	0	0	1	0	2
Alopecia	2	2	0	1	0
Headache	1	2	0	1	0
Suspected septicaemia	0	2	0	0	1
Pain	0	2	0	0	1
Constipation	0	1	0	2	1
Abdominal pain	1	0	0	2	0
Death†	0	0	0	2	0

* Includes mucositis, stomatitis, throat ulcers, mouth sores, erythematous fauces and candidiasis. † Causes of death were progressive lung metastases and apparent lung infection, respectively.

neutrophil count curve was significantly smaller with 5 or 10 μg/kg lenograstim than with vehicle.

Recovery of neutrophil counts for patients receiving chemotherapy on a single day (n = 35) and for those receiving chemotherapy over a more prolonged period (n = 29) is shown separately in Figure 2a, b. It should be noted that median neutrophil counts are shown in this figure, as opposed to the mean neutrophil counts shown in Figure 1. In each case, day 1 refers to the day on which lenograstim or vehicle was commenced, i.e. 24 h after the completion of delivery of myelosuppressive agents.

The dose-dependent effect of lenograstim is apparent in both groups of patients. Following single-day chemotherapy, the median neutrophil count was normal or supranormal by day 10 of lenograstim treatment for patients receiving ≥5 μg/kg lenograstim, but remained depressed in those receiving ≤2 μg/kg or vehicle. For patients receiving more prolonged chemotherapy, the median neutrophil count had also recovered to normal by day 10 among patients who received ≥2 μg/kg lenograstim, while the median neutrophil count remained low at this time in those receiving 0.5 μg/kg lenograstim or vehicle.

It was only a secondary aim of this dose-finding study to examine differences between treatment groups in infection rates. It was noted that a total of 17 patients (26%) had at least one clinically or microbiologically documented infection during the 18-day study period, and the overall infection rates were 3/13 (23%) in the group treated with vehicle compared with 14/53 (26%) in those receiving lenograstim.

Safety

Safety results are based on data from all 66 patients. Overall, 39 patients reported one or more clinical adverse events during the observation period (Table 3). The three most commonly reported adverse events were nausea, infection/inflammatory disorder of the buccal cavity, and insomnia. The incidence of clinical adverse events considered by investigators to be possibly, probably or highly probably related to the study medication was 0% in the vehicle, 0.5 and 5 μg/kg groups and 8 and 33% in the 2 and 10 μg/kg groups, respectively.

13 patients experienced serious adverse events (2 in the vehicle group, 4 in the lenograstim 0.5 μg/kg group, 1 in the lenograstim 2 μg/kg group, 3 in the lenograstim 5 μg/kg group, and 3 in the lenograstim 10 μg/kg group). However, in all cases, the serious adverse event was considered by the investigator to be either unrelated or only remotely related to the study medication. 2 patients, both from the lenograstim 5 μg/kg treatment group, died during the post-treatment period of the study. The causes of death were attributed to progressive lung metastases and lung infection, respectively. Both deaths were considered by the investigator to be unrelated to lenograstim treatment.

The effects of lenograstim were highly specific for recovery of neutrophil counts. Compared with vehicle, lenograstim had no clinically important effect on platelet count recovery, red blood cell (RBC) counts, or any other blood cell parameters.

There were no differences noted in the tumour response rate among patients treated with lenograstim or vehicle [38% (16/42) versus 33% (4/12) total response rate].

DISCUSSION

The aim of this dose-ranging study was to evaluate the ability of supportive treatment with lenograstim to stimulate neutrophil response in patients who had solid cancer or lymphoma and who were likely to experience chemotherapy-related neutropenia.

Results indicated that subcutaneously administered lenograstim at dosages of 0.5, 2, 5 and 10 μg/kg/day was safe and generally well-tolerated. Lenograstim was shown to stimulate neutrophil response specifically; other haematological parameters were not affected by lenograstim administration.

Lenograstim, at dosages of 0.5, 2, 5 and 10 μg/kg/day, shortened the duration and reduced the severity of neutropenia, as expressed by AUC of neutrophil counts, in patients with solid cancer or lymphoma, in a dose-dependent manner. The median duration of neutropenia was 2 or 3 days in groups treated with lenograstim, compared with 8.5 days in the vehicle group ($P < 0.05$), and the median total area under the ANC curve was higher in the lenograstim treatment groups (range 81–233) than in the vehicle group (29). These results are consistent with other phase I/II studies which have documented the dose-dependent ability of rG-CSF to decrease the severity of granulocytopenia following standard chemotherapeutic regimens in patients with small cell lung cancer [3], advanced malignancy [8] and urothelial cancer [9, 10]. The results also correspond well with those of Eguchi and associates [11], who reported a significant decrease in

the duration of neutropenia with escalating dosages (50–800 μg/m²) of rG-CSF administered intravenously for 14 days in 39 patients with advanced pulmonary cancer who were being treated with intensive chemotherapy. It has also been shown that rG-CSF dose-dependently shortened the duration of severe granulocytopenia following a chemotherapeutic regimen of cisplatin/etoposide/cyclophosphamide at doses which usually require bone marrow transplantation [12]. More recently, Linch and associates [13] have demonstrated a dose-related neutrophil response to lenograstim in bone marrow transplant patients.

The dose-dependent effect on time to recovery of neutrophil counts is clearly shown in Figure 2a, b. These results suggest that the intervals between cycles of commonly used myelosuppressive drugs could be reduced, provided that other toxicities do not preclude this. Acceleration of chemotherapy might improve the efficacy of treatment. Reduction of the overall duration of treatment might be beneficial in terms of quality of life. Further studies are needed to address both of these possibilities.

In the present study, the incidence of clinically or microbiologically documented infections was comparable among the five treatment groups. However, only 17/66 patients (26%) developed infections, possibly because of the relatively low degree and short duration of neutropenia in all treatment groups. 13 of these patients experienced infection 4–10 days after chemotherapy when the neutrophil count was low, and when lenograstim treatment-related increases in the neutrophil level would not be expected to exert an effect on susceptibility to infection. Larger placebo-controlled double-blind studies would better examine this parameter.

In conclusion, all doses of lenograstim were effective in restoring neutrophil counts in a dose-dependent manner. Lenograstim 0.5 μg/kg/day was statistically different from vehicle for median duration of neutropenia (ANC $< 1.0 \times 10^9$/l) and area under the ANC curve, while a dose of 2 μg/kg/day, in addition, shortened the time to ANC nadir. A dosage of 5 μg/kg/day also significantly decreased the total area of neutropenia ($<1.0 \times 10^9$/l) and gave the narrowest range of values for all neutrophil parameters. A dosage of 10 μg/kg/day gave unnecessary hyperleukocytosis with no additional benefit in terms of neutrophil recovery. Lenograstim 5 μg/kg/day was, therefore, chosen for further phase III clinical trials.

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