As in all forms of pleurodesis, drainage of the intracavitary space to dryness before instillation of the sclerosant is essential in reducing the likelihood of failure of primary therapy and subsequent recurrent effusions.

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Recombinant Granulocyte Colony Stimulating Factor Reduces the Infectious Complications of Cytotoxic Chemotherapy

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The aim of this study was to determine the usefulness of recombinant human granulocyte colony stimulating factor (r-metHuG-CSF) following conventional chemotherapy for small cell lung cancer. 130 previously untreated patients were randomised to receive either r-metHuG-CSF (230 μg/m²) or placebo on days 4–17 following CDE (cyclophosphamide, doxorubicin and etoposide) chemotherapy. Over all cycles, 53% of 64 patients on placebo and only 26% of 65 patients on r-metHuG-CSF had at least one experience of neutropenia with fever defined as a neutrophil count less than 1.0 × 10^9/l and a temperature ≥ 38.2°C ($P < 0.002$). It resulted in a reduction in the requirement for parenteral antibiotics from 58% in placebo patients compared with 37% in the r-metHuG-CSF group ($P < 0.02$), and a significant reduction in the incidence of infection-related hospitalisation. Chemotherapy doses were reduced by 15% or more at least once in 61% of the placebo group compared with 29% in the r-metHuG-CSF group ($P < 0.001$). 47% of the patients treated with placebo and 29% of the patients treated with r-metHuG-CSF experienced at least one cycle with a delay of 2 days or more in the administration of chemotherapy ($P < 0.04$). r-metHuG-CSF was well tolerated. There were no significant differences between the two groups in terms of response or survival.
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INTRODUCTION

ONE APPROACH to the optimisation of chemotherapy in small cell lung cancer (SCLC) is the use of relatively dose-intensive combination regimes [1]. Using such treatment, the main dose-limiting toxicity is neutropenia which carries an associated risk of infection-related morbidity and mortality, despite the use of systemic broad spectrum parenteral antibiotics [2–5]. Infectious complications, as well as hospital re-admissions, severely affect the quality of life in such patients whose prognosis remains relatively poor [6]. Furthermore, chemotherapy-induced marrow aplasia often determines treatment delays and/or reductions which might compromise therapeutic results.

Recombinant granulocyte colony stimulating factor (r-metHuG-CSF) is a glycoprotein which stimulates granulocyte

neutrophil production *in vivo*. Phase I/II studies with r-metHuG-CSF have shown that within 4–5 h of administration there is a substantial, dose-dependent increase in peripheral blood neutrophil counts [7–9]. These preliminary studies also showed that treatment with r-metHuG-CSF following cancer chemotherapy resulted in a reduction in the days of neutropenia and the treatment was well tolerated.

The present study was conducted in a population of SCLC patients and was designed to confirm, under double-blind, placebo controlled conditions, the potential clinical benefits of accelerated neutrophil recovery induced by r-metHuG-CSF. The study design allowed for comparison of the effects of r-metHuG-CSF against placebo, without cross-over, for up to six cycles of chemotherapy.

PATIENTS AND METHODS

Patients with previously untreated, histologically confirmed, SCLC (limited or extensive disease), an ECOG performance status of 0, 1 or 2, absence of evidence of infection, and normal peripheral blood indices, were eligible for entry into the study. Limited disease was defined as confined to one hemithorax with or without ipsilateral, supraclavicular or scalene lymph nodes, or contralateral mediastinal disease on computer tomography scan, and with no evidence of pleural effusion on chest X-ray. Patients receiving antibiotics, steroids or other medication likely to affect white cell counts were excluded. 130 patients were recruited from 13 centres in Europe. The study was approved by all the local ethics committees and patients gave written informed consent.

Patients were randomised to receive either r-metHuG-CSF or placebo together with chemotherapy (cyclophosphamide 1 g/m^2 day 1, doxorubicin 50 mg/m^2 day 1, etoposide 120 mg/m^2 days 1–3) for up to six 21-day cycles according to the treatment schedule shown in Fig. 1. On day 4 (i.e. 24 h after the last dose of etoposide) each patient received either r-metHuG-CSF (230 μg/m^2/day) or placebo (vehicle: 10 mmol/l sodium acetate, 5% mannitol, 0.004% Tween 80) subcutaneously in alternating left and right sites for a maximum of 14 days during each cycle (study medication could be discontinued when the postnadir neutrophil count exceeded 10 × 10^9/l after day 12 and before day 17 as indicated in Fig. 1). The principal end-point was the incidence of fever in association with neutropenia, defined as an absolute neutrophil count (ANC) less than 1.0 × 10^9/l and an oral temperature greater than or equal to 38.2°C.

Secondary end-points were to determine the effects of r-metHuG-CSF on duration and severity of neutropenia, use of antibiotics, duration of hospitalisation in this setting, tumour response rates, survival and delivery of cytotoxic therapy. Identical dose modification criteria for the cytotoxic agents were applied to both the placebo and r-metHuG-CSF treatment groups. These were:

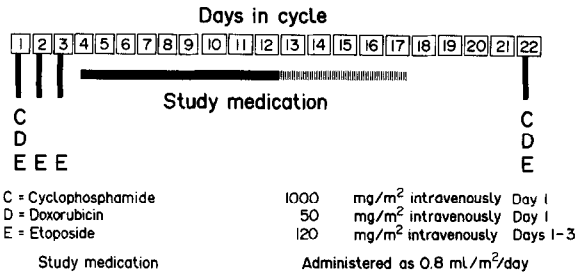

Fig. 1. Cytotoxic CDE chemotherapy was given every 21 days. Study medication, given as a volume of 0.8 ml/m^2 was started on day 4. Study medication was given until the ANC was greater than 10 × 10^9/l or for a maximum of 14 days. For patients receiving r-metHuG-CSF, the volume of 0.8 ml/m^2 corresponded to a dose of 230 μg/m^2. Study medication was administered for a minimum of 9 days (days 4–12) and for a maximum of 14 days (days 4–17). If, after day 12, the ANC count exceeded 10 × 10^9/l, then study medication was stopped.

(i) A 25% dosage reduction on days 1–3, if neutropenic fever or World Health Organization (WHO) grade 4 toxicity occurred during the previous cycle.

(ii) A 50% dosage reduction if the ANC was less than 0.1 × 10^9/l or the platelet count was less than 20 × 10^9/l for 6 days or longer during the previous cycle. A 50% reduction was also made if a second consecutive WHO grade 4 toxicity occurred during the following cycle.

(iii) At the start of each cycle, if the ANC was less than 2.0 × 10^9/l or if platelets were less than 100 × 10^9/l and this was not attributable to bone marrow involvement, chemotherapy was delayed by 7 days: the doses of chemotherapy were reduced by 75% if the ANC was 1.99–1.5 × 10^9/l and/or the platelet count was 99–75 × 10^9/l, or by 50% if the ANC was 1.49–1.0 × 10^9/l and/or the platelet count was 74–50 × 10^9/l. In the event that the ANC was less than 1.0 × 10^9/l or if the platelet count was less than 50 × 10^9/l then treatment was delayed until the ANC and/or platelets had recovered to above these levels and the next cycle of chemotherapy was given at 50% of the scheduled dose. After each modification, the patient was re-assessed and, if clinically indicated, the dose of chemotherapy was increased at the next cycle to the previous level.

Patients kept daily records of oral temperatures and drug administration, and were requested to have complete blood counts taken three times per week. Patients who developed fever ≥ 38.2°C with neutropenia < 1.0 × 10^9/l were hospitalised and were treated with parenteral antibiotics. Guidelines for antibiotic therapy were written in the study protocol, however, the final decision about the choice of antibiotic was at the discretion of the treating physician. Antibiotic treatment was discontinued when the patient had a temperature less than 38.2°C for 24 h or more and there was no clinical evidence of infection. Daily blood counts were taken until fever, neutropenia and/or infection had resolved. At the completion of a treatment cycle in which the first event involving concurrent neutropenia and fever occurred,

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Other participants include
C. Williams at Southampton General Hospital, Southampton, U.K.; A. van Oosterom at Universitair Ziekenhuis, Edegem, Belgium; B. Hancock at Weston Park Hospital, Sheffield, U.K.; R. Mertelsmann at Med University Klinik, Freiburg, Germany; and F. Cavalli at Bellinzona, Switzerland.
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Table 1. Patient's characteristics

		Placebo (n = 64) (%)	G-CSF (n = 65) (%)
Median age (years)		60	58
Sex	Male	44 (69)	45 (69)
ECOG*	0	24 (37)	22 (34)
	1,2	40 (63)	43 (67)
Stage	Limited	25 (39)	22 (34)
Marrow involved		8 (12)	8 (12)

*Eastern Co-operative Oncology Group—performance status.

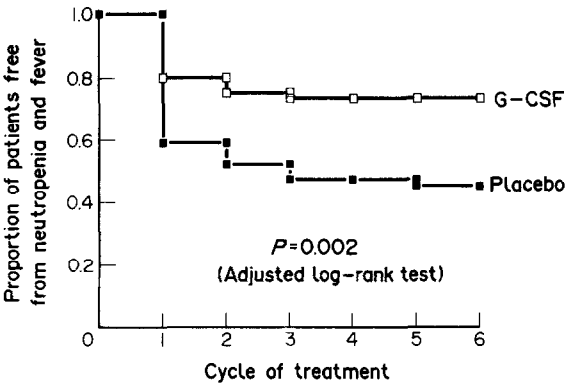

Fig. 2. Proportion of patients in each treatment group who did not experience at least one episode of fever concurrent with neutropenia (ANC less than 1.0 × 10⁹/l and fever ≥ 38.2°C). Data shown by cycle.

study drug was unblinded. If a patient was receiving r-metHuG-CSF, treatment was continued on an open basis; if the patient was receiving placebo, no further injections were given. Patients randomised to placebo were not crossed over to receive r-metHuG-CSF at any stage.

During all cycles patients were observed for other clinically significant events. Tumour response rates were documented according to WHO criteria, following two cycles of chemotherapy and on completion of the study. Chemotherapy was continued after two cycles only in patients showing evidence of objective (partial or complete) response. Patients with stable or progressive disease were withdrawn from the study and further treatment was at the discretion of the treating physician. All patients were subsequently followed for evidence of relapse and survival outcome.

The calculated sample size for the study was based upon the expectation of detecting a 60% reduction in the incidence of the primary end-point (concurrent fever and neutropenia) in the treated population with a type 1 error level of 0.05 using a two-sided test and 80% power in a multicentre setting.

All statistical tests were conducted adjusting for the effects of study centre, and disease status at study entry. Initial primary variable event rates (neutropenia with fever) were compared using the Mantel–Haenzel χ^2 test. Time to first event of concurrent fever and neutropenia was estimated using stratified Kaplan–Meier [10] time-to-event analysis.

Chemotherapy dose intensity was expressed in mg/m²/week and calculated as the ratio between the prescribed and the achieved dose for each of the three drugs [11].

RESULTS

A total of 130 patients were randomised to receive placebo (n = 64) or r-MetHuG-CSF (n = 66). Of these, all were evaluable in the placebo group and 65 in the r-metHuG-CSF group. 1 patient was not evaluable because he died before receiving chemotherapy. The characteristics of the patients (Table 1) indicate that both groups were comparable at randomisation. Of those treated for the full six cycles, 45 patients received placebo and 44 received r-metHuG-CSF.

Over all cycles, the proportion of patients developing at least one episode of neutropenia associated with fever was 53% (34/64) in the group receiving placebo compared with 26% (17/65) in the r-metHuG-CSF group ($P < 0.002$). In cycle one, the respective figures were 41% for placebo-treated patients and 20% in r-metHuG-CSF-treated patients ($P < 0.012$). Fig. 2 shows these data presented as time-to-event curves ($P < 0.002$). The total number of events of neutropenia associated with fever was 49 in the placebo group compared with 26 in the r-metHuG-CSF group.

The median duration of neutropenia (ANC < 1.0 × 10⁹/l) was 3 days in cycle one but less than 1 day for all other cycles in the r-metHuG-CSF group, while in the placebo group it ranged from 9 to 11 days ($P < 0.001$). The median total days of neutropenia, over all six cycles, in this study was 6 days in the r-metHuG-CSF group, but 15 in the placebo group. In the

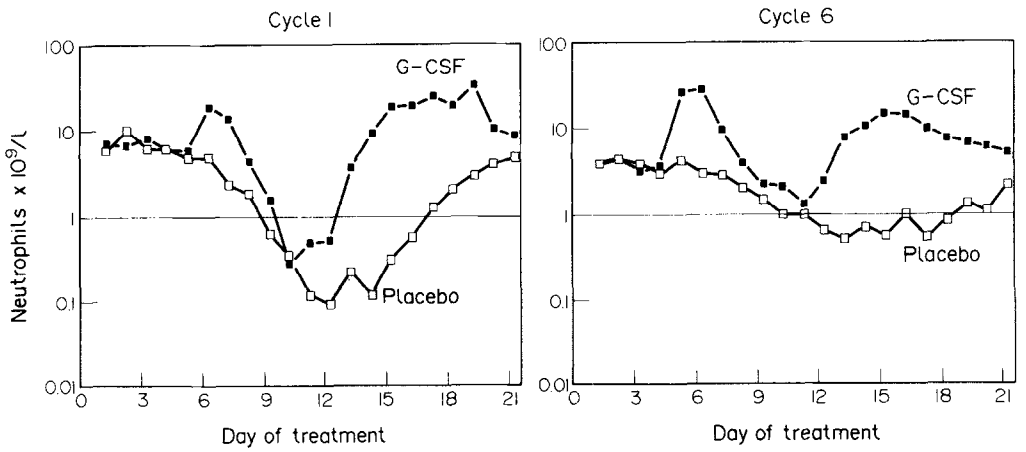

Fig. 3. Neutrophil profiles for both treatment groups shown for cycles one and six.

r-metHuG-CSF group the median ANC nadir in cycle 1 was 0.42×10^9/l, but was consistently greater than 1×10^9/l in all other cycles. In the placebo group the first cycle median ANC nadir was 0.09×10^9/l with a range of $0.25–0.45 \times 10^9$/l in all other cycles. Figure 3 shows neutrophil profiles for cycles 1 and 6.

The apparent incidence of bone marrow infiltration was low in this study, with only 8 patients in each group reported to have bone marrow involvement at presentation. These small numbers make it impossible to make any statistically valid comparisons about the effect on bone marrow involvement on the efficacy of r-metHuG-CSF. However, review of the data from these patients showed a similar neutrophil response to r-metHuG-CSF in patients with reported bone marrow involvement compared with those without marrow infiltration. The incidence and median duration of neutropenia being 63 and 58% and 2 days and 1 day in the bone marrow-positive and bone marrow-negative groups, respectively. In addition, bone marrow-positive patients treated with r-metHuG-CSF had a reduced duration of neutropenia when compared with placebo-treated patients with reported bone marrow infiltration (median duration of 2 vs. 7.5 days, respectively).

Significantly more patients in the placebo-treated group required at least one course of intravenous antibiotics (i.e. 58% placebo and 37% r-metHuG-CSF, $P < 0.02$). In addition, 58% of the placebo-treated patients needed to be hospitalised for infection-related causes compared with 39% of the r-metHuG-CSF treatment group ($P < 0.04$). The incidence of culture-confirmed infections was 33% of placebo-treated patients and 20% of r-metHuG-CSF-treated patients, having detectable positive bacterial cultures ($P = 0.101$). In addition, there were three infection-related deaths in the placebo group and one in the r-metHuG-CSF group.

The proportion of patients who required a 15% or greater reduction in their target dose of cyclophosphamide, doxorubicin or etoposide during cycles 2–6 is shown in Fig. 4a. In each cycle approximately 40–50% of patients receiving placebo had a dose reduction compared with less than 20% of patients who were receiving r-metHuG-CSF. Over all cycles, 61% of patients randomised to placebo had at least one dose reduction compared with 29% of the r-metHuG-CSF patients ($P < 0.001$). Fig. 4b illustrates the percentage of patients who experienced a dose delay of 2 days or more. In cycle 2, equal percentages of patients randomised to placebo or r-metHuG-CSF experienced a dose delay. However, during cycles 3–6 approximately 25% of patients randomised to placebo had a dose delay compared with 11–16% on r-metHuG-CSF. Over all cycles, 47% of those on placebo had at least one cycle that was dose delayed compared with 29% of those in the r-metHuG-CSF group ($P < 0.04$). As a result of these differences in dose delays and dose reductions, the patients on r-metHuG-CSF received a greater dose intensity than those on placebo. These data are shown in Table 2.

The overall response rates were similar, being 79% in the group treated with r-metHuG-CSF and 87% in the placebo group. There was no evidence of any significant difference in survival between the r-metHuG-CSF and the placebo group. The median survival in patients with extensive disease was 8.9 months in the r-metHuG-CSF arm and 9.5 months in the placebo arm. In the limited-disease group, the median survival was 13.9 months in the r-metHuG-CSF arm and 12.8 months in the placebo arm.

The depth of thrombocytopenia and the degree of anaemia became worse with each cycle. There were no differences in the

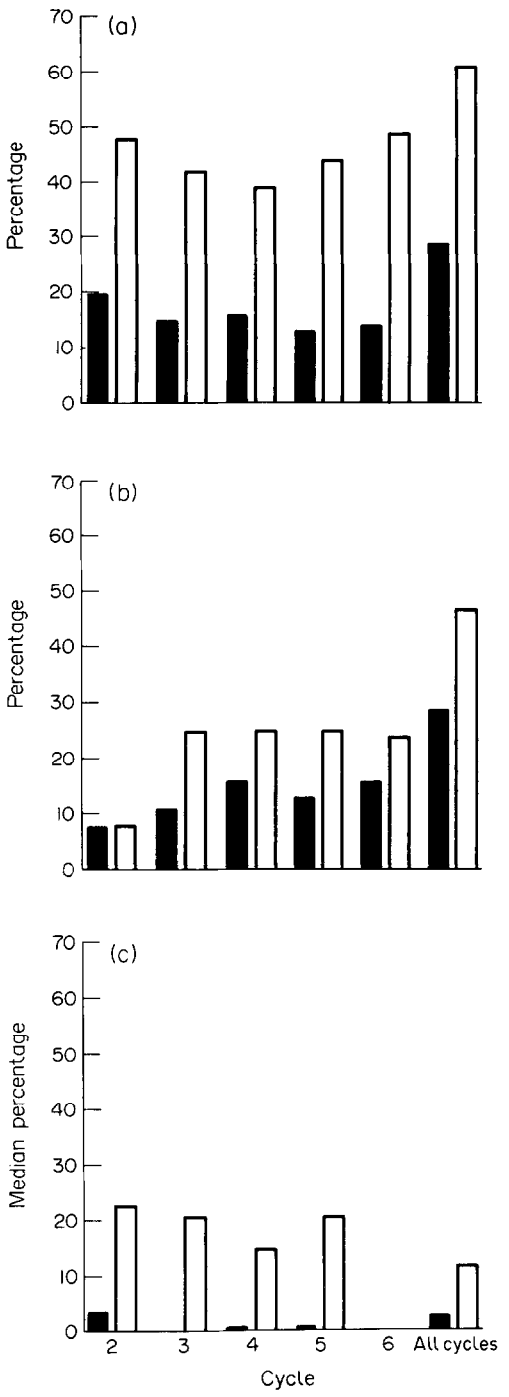

Fig. 4. (a) Percentage of patients with a dose reduction of 15% or greater shown by cycle and over all cycles for r-metHuG-CSF-treated patients (solid) vs. placebo-treated patients (clear). (b) Percentage of patients with a dose delay of 2 days or more shown by cycle and over all cycles for r-metHuG-CSF-treated patients (solid) vs. placebo-treated patients (clear). (c) Median percentage of patients with reduced cyclophosphamide dose intensity by cycle and over all cycles for r-metHuG-CSF-treated patients (solid) vs. placebo-treated patients (clear). Dose intensity was not calculated for cycle 6 as this was the final cycle of treatment so the duration over which chemotherapy was delivered could not be defined. Data for cycle 1 are not shown since by protocol definition, all patients received full dose on-time in the first cycle.

Table 2. Median dose intensity of chemotherapy

	CDE dose prescribed (mg/m²/week)	CDE dose achieved (placebo)	CDE dose achieved (G-CSF)*
Cyclophosphamide	333.3	292 (87.7%)	321 (96.1%)
Doxorubicin	16.7	15 (89.4%)	16 (96.0%)
Etoposide	120.0	105 (87.8%)	115 (95.7%)

*Difference between dose of CDE delivered on placebo and G-CSF significant at the level $P < 0.05$.
100% dose intensity = 100% target dose in 138 days.

profiles of either variable between the placebo- and r-metHuG-CSF-treated patients in the first cycle. The platelet nadirs were lower in the r-metHuG-CSF-treated group during cycles 2–6 with the most pronounced effect seen in cycle 6 (Fig. 5). These differences were possibly related to the greater dose intensity of chemotherapy. They were not associated with an increased incidence of haemorrhagic complications.

The incidence of clinical adverse events recorded from both treatment groups in blinded cycles was similar except for reports of musculoskeletal pain where, in the r-metHuG-CSF-treated group, the reported incidence was 15% of patients whilst in the placebo-treated group it was 9%. Simple analgesics were found to control the symptoms in all patients and in no patient did this complaint lead to interruption of treatment. Other adverse events reported in both arms of the study included alopecia, nausea, vomiting, stomatitis and diarrhoea. These are likely to be a consequence of cytotoxic chemotherapy.

DISCUSSION

The major finding of this study was that the administration of r-metHuG-CSF as an adjunct to cyclophosphamide, doxorubicin and etoposide chemotherapy for SCLC significantly reduces the duration and severity of neutropenia and associated clinical sequelae. Reductions in the proportions of patients hospitalised with evidence of infection, and those given antibiotics were significant. This reduction of neutropenia-related infectious complications was felt to substantially improve the tolerance of the treatment and, therefore, the quality of life in these patients. However, the number of patients in the study was not sufficient to show if this reduction would also result in a decrease in mortality.

R-metHuG-CSF was well tolerated and the most frequently reported side-effect attributed to its administration was mild to moderate musculoskeletal pain, which was never dose limiting and always controlled with simple analgesia. The lower platelet nadirs seen in patients receiving r-metHuG-CSF compared with placebo particularly in the sixth cycle were not associated with any clinically important bleeding episodes, and are thought to be a consequence of the greater total dose of chemotherapy delivered to the r-metHuG-CSF group.

Studies *in vitro* using granulocyte colony stimulating factor have reported receptors and/or clonal growth stimulation in cell lines derived from a variety of solid tumours, including SCLC [12]. A comparison of the response rates and survival in this study showed no difference between the groups receiving r-metHuG-CSF or placebo and no evidence of any detrimental effect of r-metHuG-CSF on tumour response.

It is possible to compare the results of this study with the results of a study conducted in the USA in which the doses of r-metHuG-CSF and chemotherapy were identical [13]. R-metHuG-CSF induced a similar reduction in the incidence of neutropenic fever in both studies. However, the incidence of neutropenic fever was higher in both placebo and r-metHuG-CSF groups in the previous study (77 vs. 50%) than in the present study (53 vs. 26%), an effect which may be related to differences in patient selection. However, the percentage reduction in the incidence of neutropenic fever in both studies was similar and suggests benefit for patient populations exposed to a risk of chemotherapy-induced haematological toxicity. This benefit may not be so apparent where the chemotherapy used produces less severe haematological toxicity.

The American study design [13] differed in that patients on the placebo arm who experienced neutropenia concurrent with fever were unblinded and then received open label r-metHuG-CSF. This cross-over between the two arms raised difficulties in the interpretation of response, toxicity and dose-intensity data. However, both studies allowed for comparison of the effects of r-metHuG-CSF under double-blind conditions and show highly significant reductions in infection rates (defined as ANC $< 1 \times 10^9$/l with fever $\geq$ 38.2°C), along with related reductions in antibiotic use and infection-related hospitalisation.

In this study the reduction in culture-confirmed infections was similar to that seen in the reduction in neutropenia associated with fever. The low rate of documented infection is a consequence of the difficulties related to confirming infections in cases

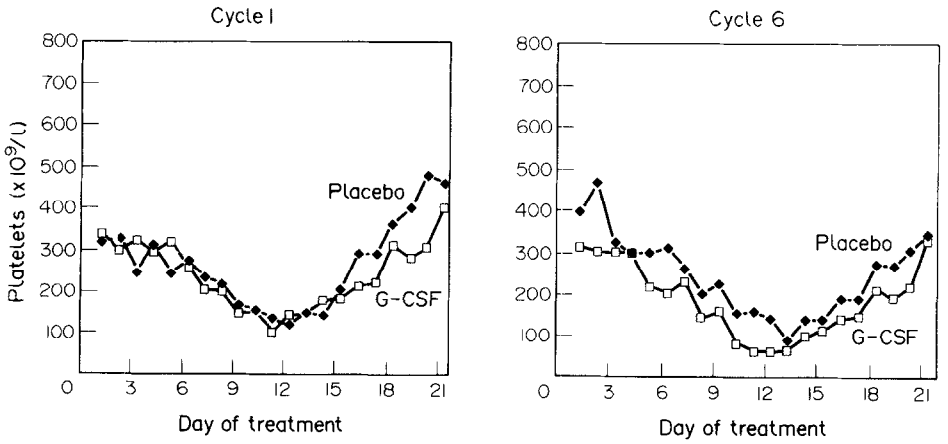

Fig. 5. Platelet profiles for both treatment groups shown for cycles 1 and 6.

of febrile neutropenia. Only 40–50% of patients with fever and neutropenia are found to have positive bacterial cultures and after initiation of antibiotic therapy, cultures are usually negative [14, 15]. This low frequency makes it difficult to show statistically significant differences in culture-confirmed infection rate.

It is interesting to note (Fig. 3) that in both r-metHuG-CSF- and placebo-treated patients the neutrophil nadir was lower in cycle 1 than in cycle 6. Although this reduction was seen in successive cycles in both groups, patients receiving r-metHuG-CSF always had less neutropenia compared with the placebo group. This progressive reduction in nadir is likely to be due to patient selection, with fitter, better performance status patients receiving a greater proportion of the planned six cycles of chemotherapy. It may also be due, in part, to successive dose reductions from cycle 1 to 6, which occurred in both groups (though less in the r-metHuG-CSF group) or to the priming effect on multipotential progenitor cells in the bone marrow of patients receiving successive cycles.

Patients receiving r-metHuG-CSF were also able to receive a higher proportion of their chemotherapy without dose reduction or delay. It is unlikely, however, that the modest increase in dose intensity seen in this study would be sufficient to impact upon disease response or survival, and indeed, a recent meta-analysis in SCLC on the impact of dose intensity in various conventional chemotherapy regimens has shown no correlation with outcome for the majority of them [16]. A secondary aim of the study was to assess the effect of r-metHuG-CSF on chemotherapy dose delivery, the intention being to achieve full dose-on-time administration, rather than any attempt to increase the absolute dose or reduce the cycle length. These results indicate that r-metHuG-CSF may have a role in facilitating the delivery of chemotherapy at reduced intervals or increased dose, but in this setting the use of r-metHuG-CSF needs to be fully evaluated in appropriately designed clinical trials with awareness that toxicities other than neutropenia may become dose limiting. Potential problems relating to increased dose include thrombocytopenia and data from the present study illustrate that even with quite modest increases in dose intensity, an effect on platelets can be observed.

This study has shown that r-metHuG-CSF is well tolerated and effective in reducing the morbidity associated with chemotherapy-induced neutropenia, and also has the potential to increase the amount of cytotoxic chemotherapy that can be administered per unit time.

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