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A PHASE I TRIAL TO ASSESS THE VALUE OF RECOMBINANT HUMAN GRANULOCYTE COLONY STIMULATING FACTOR (R-MeTHuG-CSF, FILGRASTIM) IN ACCELERATING THE DOSE RATE OF CHEMOTHERAPY FOR INTERMEDIATE AND HIGH-GRADE NON-HODGKIN'S LYMPHOMA (NHL)

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SUMMARY

In a multi-centre phase I study we investigated the possibility of reducing the interval between courses of standard CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 2 mgs day 1, and prednisolone 40 mg/m^2 days 1–8) from 21 days to 15 days and then 10 days using granulocyte colony stimulating factor (r-MetHuG-CSF (Amgen)-filgrastim) to accelerate neutrophil recovery. Patients received CHOP followed by G-CSF 5 μg/kg s.c. from day 2 to the day before the next course (e.g. days 2–14 for the 15-day interval). A total of 28 patients with newly diagnosed intermediate grade or high grade NHL were studied. Four patients were studied at a 21-day interval, six patients were treated at a 15-day interval and subsequently six patients at a 10-day interval. Following analysis of this initial cohort, a further 12 patients were evaluated; four at the 15-day interval, and eight at the 10-day interval. No dose-limiting toxicity was seen in the four patients receiving 21-day CHOP. Dose-limiting toxicity was seen in 4/10 patients treated at the 15-day interval (M:F 7:3, median age 55·5, range 39–67 years). This consisted of infection in two patients, recurrent infection and debility in a third, and mucositis in a fourth. Seven patients experienced one or more infectious episodes requiring antibiotics (median number of episodes: 2, range 1–4). Fourteen patients (M:F 4:3, median age 47·5, range 25–63 years) were treated at the 10-day interval. Dose-limiting toxicity was seen in six patients. This consisted of severe mucositis in three patients, neutropenia and thrombocytopenia on two separate occasions in one patient, and steroid-induced gastritis in two patients. Nine patients had one or more documented infections (median: 2, range 1–3) requiring antibiotics, of which six were severe (WHO grade 3 or 4). One patient died of *Pneumocystis carinii* (PCP) pneumonia. In summary, G-CSF (filgrastim) will facilitate the shortening of the dosage interval between cycles of CHOP chemotherapy due to accelerated hematological recovery. However, non-hematological toxicity due to the shorter dosage interval is increased and infective episodes are frequent.

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KEY WORDS CHOP; G-CSF; dose interval

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INTRODUCTION

High grade NHL is potentially curable with combination chemotherapy, and dose intensity isimportant in outcome.[1] CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone) was one of the first regimens used in this disease and approximately 30 per cent of patients will be cured following this treatment.[2] Second and third generation regimens, such as MACOP-B, have been reported as giving response rates as high as 84 per cent[3] but randomized comparisons have shown that such dose intensive schedules do not achieve significantly better overall survival rates than CHOP.[4] In addition they are invariably more toxic, the most important dose-limiting effect being myelosuppression. There is some evidence that dose rate may be an important determinant of response to treatment and outcome in young people with high grade NHL,[5] and hence a regimen delivering standard CHOP at an increased frequency may be valuable. Granulocyte-colony stimulating factor (G-CSF) reliably promotes the growth and differentiation of myeloid precursors leading to early neutrophil release.[6,7] It has been clearly shown to obviate chemotherapy induced neutropenia,[8–10] and hastens the recovery of neutrophils following autologous bone marrow transplantation (ABMT).[11] In the treatment of lymphoma, G-CSF might be used to reduce the extent and duration of neutropenia following chemotherapy, or to facilitate dose intensification. It was this latter approach that was investigated in this pilot study.

PATIENTS

Entry criteria

Previously untreated patients between 18 and 75 years of age with histologically proven high-grade non-Hodgkin's lymphoma (Kiel classification)[12] for whom chemotherapy was thought appropriate were eligible for inclusion. Prior treatment with a single regimen of radiotherapy for stage I disease was allowed.

Patients were required to have an absolute neutrophil count $\geqslant 2{\cdot}0 \times 10^9$/l, a platelet count $\geqslant 100 \times 10^9$/l and normal renal function (serum creatinine of less than 120 μmol/l and urea of less than 8 mmol/l). Aspartate aminotransferase (AST, SGOT) alanine aminotransferase (ALT, SGPT) and alkaline phosphatase were required to be less than 2·5 times the upper limit defined at the investigating laboratory. Exclusion criteria included pregnant or lactating women, any patient with primary central nervous system (CNS) disease or symptoms suggestive of CNS involvement, and patients with a history of a second malignancy. Patients with severe cardiac conditions or any other serious medical or psychiatric illness preventing informed consent or intensive treatment were also excluded, as were patients with clinical or bacteriological evidence of infection.

TREATMENT

All patients received CHOP chemotherapy in the following doses:

Cyclophosphamide 750 mg/m^2 i.v.	day 1
Hydroxydaunorubicin 50 mg/m^2 i.v.	
Vincristine 2 mg i.v.	
Prednisolone 40 mg/m^2 days 1–7	

followed by granulocyte-colony stimulating factor (R-MetHuG-CSF-filgrastim) at a dose of 5 μg/kg subcutaneously from day 2 to the day before the next course of chemotherapy, i.e. days

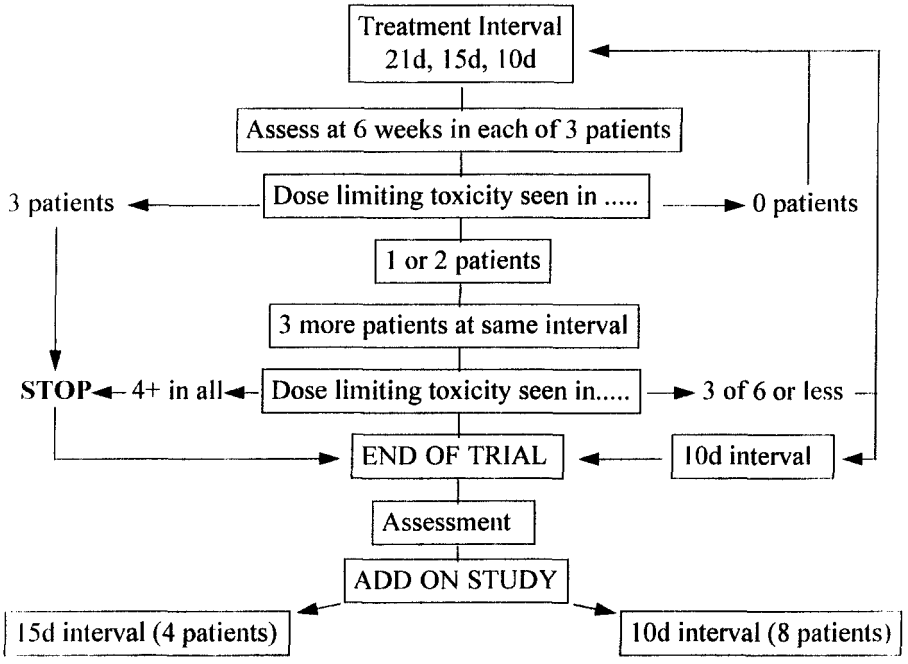

Figure 1. Study design

2–20 for the 21-day interval, days 2–14 for the 15-day interval. If after 8 days of G-CSF administration, the absolute neutrophil count (ANC) exceeded 20×10^9/l, the G-CSF was discontinued until the ANC fell below 5×10^9/l.

Study design

This was an open, sequential cohort, schedule-finding study (Figure 1). Initially a minimum of three patients were to be treated at a 21-day interval. If after 6 weeks none of these patients experienced dose-limiting toxicity, then a further three patients would be entered into the study and treated at a 15-day interval. If no dose-limiting toxicity was experienced the next cohort of patients could be treated at the 10-day interval. However, if dose-limiting toxicity was seen at either the 21-day or the 15-day interval in one or more patients, the next cohort would be entered at the same dose interval. If no more than 50 per cent of the total patients treated at this interval experienced dose-limiting toxicity after a further 6 weeks of assessment, the next cohort could be treated at the shorter dosage interval.

The study endpoints were the incidence of dose-limiting toxicity at each treatment level, the incidence of febrile neutropenia (duration and severity) documented infection and use of intravenous antibiotics.

Dose-limiting toxicity was defined as an absolute neutrophil count of $<0{\cdot}5 \times 10^9$/l for more than 4 consecutive days, a platelet count of $<25 \times 10^9$/l for more than 4 consecutive days, any WHO grade 3 or 4 non-hematological toxicity, excluding alopecia, nausea, vomiting and vincristine neuropathy,[13] and absence of recovery of ANC (to $\geqslant 1{\cdot}5 \times 10^9$/l) or platelet count ($\geqslant 50 \times 10^9$/l) at date of retreatment.

It was intended that patients who experienced such dose-limiting toxicity as defined above should have subsequent courses of chemotherapy delayed until the ANC recovered to

Table 1. Patient characteristics

	No. of patients	M:F	Age range (median)
21-day interval	4	0:4	42–64 (44)
15-day interval	10	7:3	39–67 (55·5)
10-day interval	14	4:3	25–63 (47·5)

$\geqslant 1{\cdot}5 \times 10^9$/l, the platelets recovered to $\geqslant 50 \times 10^9$/l (unsupported), or recovery from any WHO grade 3 or 4 non-hematological toxicity had occurred, but in some patients dose reductions in cyclophosphamide and adriamycin took place at the treating physician's discretion. In febrile patients treatment was delayed until the oral temperature remained <38·2°C for more than 2 h, or the administration of i.v. antibiotics had been discontinued for at least 24 h. Dose reduction (in vincristine) was allowed for vinca neuropathy. This comprised 50 per cent reduction for WHO grade 3 toxicity, and discontinuation of the drug for grade 4 toxicity.

Assessment of the tumour response to chemotherapy was made after cycle 3, and then immediately prior to cycles 5 and 7, at the end of the study and at the follow-up visit (1 month after cessation of treatment). WHO criteria for evaluation of tumour response were used.[13] Treatment was continued for a maximum of eight cycles except in patients who had achieved complete remission (CR) after three cycles in which case treatment was stopped after six cycles. Patients who demonstrated progressive disease at any point in the trial were withdrawn.

Dose intensity

Received dose intensity (DI) was projected for the various treatment cohorts based on the method originally described by Hryniuk.[14] This is based on the dose of cyclophosphamide according to the formula:

$$\text{DI (mg/m}^2\text{/ week)} = \frac{\text{Total mg of cyclophosphamide} \times \text{No. of cycles/body surface area}}{\text{Total days of therapy/7}}$$

where total days of therapy is the number of days between the first day of the first cycle and the last day of the last cycle. Based on this calculation, the projected dose intensity (PDI) for patients receiving CHOP at the three dosage intervals for a 'standard' six cycles would be: 250 mg/m^2/week for the 21-day cycle, 375 mg/m^2/week for the 15-day cycle, which represents a 33 per cent increase, and 525·2 mg/m^2/week for the 10-day interval, which represents a 48 per cent increase in PDI over CHOP given at the 21-day interval.

RESULTS

A total of 28 patients were studied (Table 1). Initially four patients were studied at the 21-day interval, six patients at the 15-day interval and six patients at the 10-day interval. Following analysis of these initial patients, the study investigators felt that not enough information regarding dose-limiting toxicity was generated by the numbers of patients entered at the shorter dosage intervals and hence a further 12 patients were recruited (in an add-on study), four at the 15-day interval and eight at the 10-day interval.

Table 2. 15-day CHOP—dose-limiting toxicity

	UPN	Cycle no.	Toxicity	Delay (days)
Infection				
	8	6	R.T.I.	7
	10	3	Staphylococcus abscess+debility	33
		5	R.T.I.	7
	19	2	Septicemia (+WHO grade 3 mucositis)	14
Mucositis				
	5	3	WHO grade 3	5

R.T.I., respiratory tract infection.

21-Day interval

A total of four patients was entered. One patient only experienced two separate delays of chemotherapy of 2 days and 7 days due to a urinary tract infection on one occasion and pyrexia of undetermined origin (not associated with neutropenia) on the second. No WHO grade 3 or 4 toxicity was seen.

15-Day interval

Ten patients were entered and dose-limiting toxicity was seen in four (40 per cent). In three of these patients, this comprised severe WHO grade 3 or 4 infection leading to a dosage delay or reduction during one or more cycles. In addition, in one of these patients (UPN 10), dose reductions took place at the treating physician's discretion. This consisted of a 15 per cent reduction in cyclophosphamide and a 25 per cent reduction in adriamycin and vincristine dosage during the sixth and seventh cycles due to general debility and, during cycle 6 only, severe oral thrush. Patient 19, who developed septicemia, was withdrawn from the study after the first course as it was felt the patient was too ill to continue at full doses of chemotherapy. A fourth patient developed severe mucositis leading to a 5-day delay following his third cycle of chemotherapy (Table 2).

The pattern of neutrophil recovery in one of the patients treated at the 15-day interval is shown in Figure 2 and was fairly typical. There was a sharp rise in the total nucleated cell count (TNCC) in the first few days following the administration of G-CSF, before falling to a nadir at about day 8. This nadir would typically be short lived, with a further brisk recovery in the TNCC, often to levels $>20 \times 10^9$/l, within 24 h.

Seven out of 10 patients treated at the 15-day interval experienced a median of two documented infections or pyrexial episodes requiring antibiotic treatment, although only one patient developed septicemia (Table 2). Other toxicity, though not dose-limiting, was also increased. Of the patients 70 per cent developed mucositis for a median of three cycles of chemotherapy, and one-third of patients developed vinca neuropathy leading to dosage reduction for a median of three cycles of chemotherapy (Table 3).

10-Day interval

Six out of 14 (43 per cent) patients entered at this dosage interval experienced dose-limiting toxicity. Three of the patients had severe WHO grade 3 or 4 mucositis leading to treatment delays, all during the latter cycles of therapy (Table 4). In addition, one of these patients (UPN

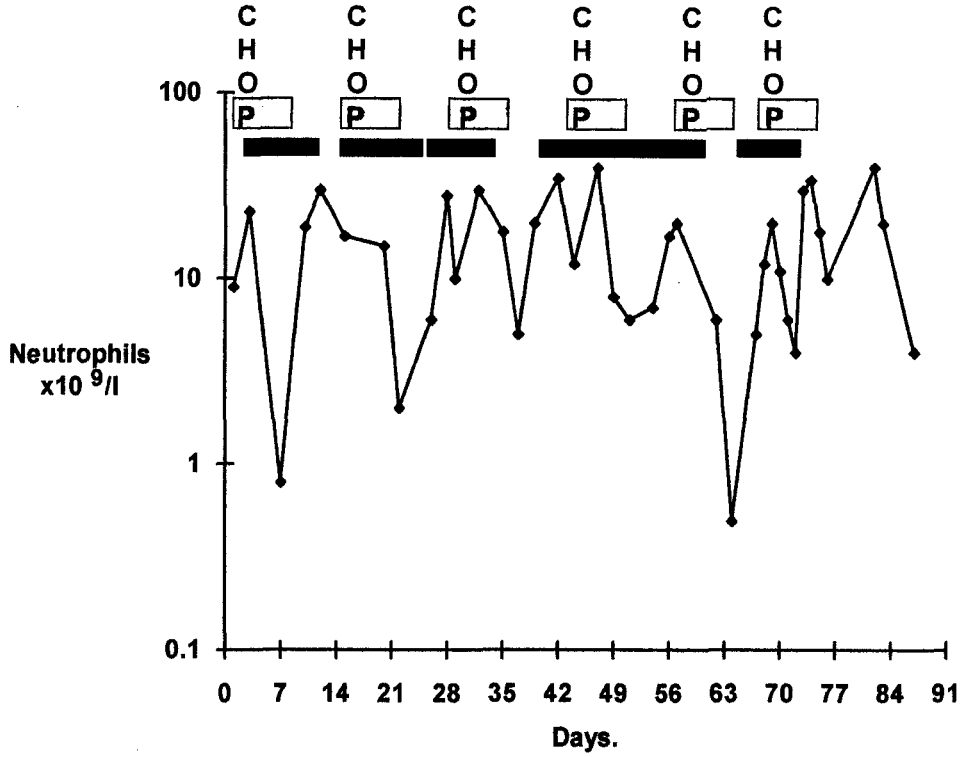

Figure 2. Pattern of neutrophil recovery in a patient treated at the 15-day interval. (■ indicates days of G-CSF therapy)

Table 3. 15-day CHOP—other toxicity

	No. of patients	Courses (median, range)
Mucositis (not dose-limiting)	7	(3, 1–5)
Vinca neuropathy (leading to dose reduction)	3	(3, 1–5)

16) had the dose of doxorubicin reduced during cycles 4 and 5 due to mucositis. In this group, dose-limiting toxicity due to myelosuppression was seen, albeit only in one patient whose neutrophil count failed to recover to $>1{\cdot}5 \times 10^9$/l by the date of next treatment on one occasion, and whose platelet count was less than 50×10^9/l by the date of the next treatment on three occasions. This same patient (UPN 29) also had three treatment delays due to severe infection. Two patients required a dose reduction in prednisolone due to severe gastritis.

Nine out of 14 patients (64 per cent) developed one or more infections or pyrexial episodes requiring antibiotic treatment (median: 2, range 1–3). The majority of infections (six out of 10) were of the respiratory tract, with only one case of septicemia. Two patients developed severe mouth ulcers, and one oropharyngeal candidiasis. One patient developed fatal *Pneumocystis carinii* pneumonia (PCP). This occurred following completion of his sixth cycle of chemotherapy

Table 4. 10-day CHOP—dose-limiting toxicity

	UPN	Course No.	Toxicity	Delay (days)
Mucositis				
	12	4	WHO grade 3/4	10
	16	4	WHO grade 3/4	13
	24	4	WHO grade 3/4	4
Neutropenia and thrombocytopenia				
	29	2	ANC<1·5 × 10^9/l	2
		5	Plts<50 × 10^9/l	6
		6	Plts<50 × 10^9/l	7
		8	Plts<50 × 10^9/l	10
Infection				
	29	3	Pharyngitis+oral ulceration	7
		4	R.T.I.	14
		7	R.T.I.	11
Steroid-induced gastritis		Dose reduction in prednisolone in two patients (UPN 17 and UPN 15) for one course and five courses respectively		

R.T.I., respiratory tract infection.

and was not associated with neutropenia. The pattern of neutrophil recovery seen in this patient was fairly typical of that seen in the patients treated at the 10-day interval (Figure 3). A nadir in the WCC was usually seen at about day 8 following chemotherapy, with satisfactory recovery by day 10.

As far as non dose-limiting toxicity was concerned 10 patients (70 per cent) experienced mucositis for the majority of their treatment (median number of courses: 4, range 1–6) and five out of 14 patients (36 per cent) required the dose of vincristine to be reduced.

Disease response

All patients treated at the 21-day interval achieved CR. Of the patients treated at the 15-day interval, four achieved CR, five achieved PR and in one patient the response was not assessable. Six out of 14 patients treated at the 10-day interval achieved CR, seven achieved PR (including the patient dying of PCP pneumonia) and disease progression was seen in one patient.

DISCUSSION

The reduction in the dosage interval between courses of CHOP achieved in this study would mean that, at the 15-day interval, the projected increase in dose intensity (DI) of 33 per cent was achieved in 60 per cent of patients and at the 10-day interval 57 per cent of patients achieved the projected 48 per cent increase in DI. However, at both the 15-day and 10-day treatment intervals the neutropenia experienced at the nadir, albeit short lived, was frequently profound, especially with later cycles of chemotherapy. Consequently, at both of the shorter treatment intervals, a similar high proportion of patients (70 per cent at the 15-day interval, 64 per cent at the 10-day interval) experienced one or more infections or pyrexial episodes during their treatment. In addition, non-hematological toxicity became dose-limiting at the shorter dosage intervals, and

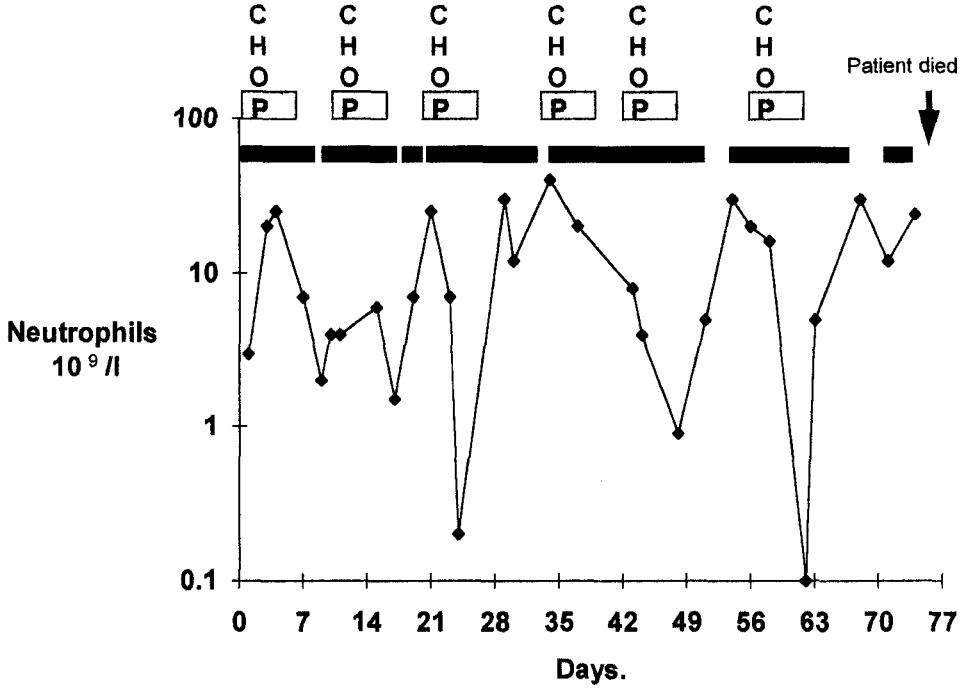

Figure 3. Pattern of neutrophil recovery in a patient treated at the 10-day interval. (■ indicates days of G-CSF therapy)

added considerably to the discomfort experienced by patients, even if not leading to treatment reduction or delay. Two-thirds of patients at the 10-day interval had mucositis for the greater part of their treatment, and a third had severe vinca neuropathy.

Other workers have demonstrated that dose intensity of chemotherapy can be increased using G-CSF, in a variety of clinical situations.[15,16] Specifically with CHOP type regimens, filgrastim has been shown to facilitate dose interval reduction (to 14 days) and increase in dosage of cyclophosphamide (by 100 per cent) and adriamycin (by 33 per cent) to increase PDI in patients with NHL.[17] The authors stated that the maximum tolerated dose was not reached in this latter study and that further dose escalation could be achieved. Similarly, filgrastim was successfully used to reduce the interval between cycles of alternating VIM (VP16, ifosfamide, methotrexate) and CHOP in patients with HG NHL from 17 days to 14 days with continued therapy in over 80 per cent of cycles.[18] In our study we have demonstrated in a systematic way that dose intensity can be further increased with a reduction in the dosage interval to 10 days.

CONCLUSIONS

This study has shown clearly that G-CSF (filgrastim) will accelerate neutrophil recovery following CHOP chemotherapy in patients with NHL. As a consequence the dosage interval can be reduced from a standard 21 days to 15 days and 10 days with no significant treatment delays due to myelosuppression. Side-effects of filgrastim are mild and well tolerated. This approach is clearly a worthwhile option for the intensification of treatment of NHL. However, shortening the dosage interval is not without associated toxicity both in terms of infection and

non-hematological effects such as mucositis. We would suggest that the 15-day interval is the most acceptable in this regard. Whether the projected increase in dose intensity consequential on applying an 'accelerated' CHOP regimen is manifested in higher CR rates and disease-free survival in high grade NHL will need to be evaluated in a prospective randomized trial.

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