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Papers

Efficacy and Tolerability of Recombinant Human Granulocyte–Macrophage Colony-Stimulating Factor in Patients with Chemotherapy-related Leukopenia and Fever

Bonne Biesma, Elisabeth G.E. de Vries, Pax H.B. Willemse, Willem J. Sluiter, Pieter E. Postmus, Pieter C. Limburg, Angelika C. Stern and Edo Vellenga

30 patients with chemotherapy-related leukopenia (white cells 1.0 × 10^9/l or lower) and fever (temperature 38.5°C or higher) were treated in a double-blind randomised trial with standard antibiotics and 7 days of intravenously administered recombinant human granulocyte–macrophage colony-stimulating factor (GM–CSF, 2.8 μg/kg per day) or placebo. GM–CSF administration resulted in a faster percentage increase of peripheral neutrophil count after 2 and 3 days of treatment, except in patients treated with ablative chemotherapy and autologous bone-marrow transplantation. However, GM–CSF did not shorten the period of fever or antibiotic administration. No side-effects were observed; in particular tumour necrosis factor alpha and interleukin-6 did not increase in the 5 GM–CSF patients tested. These data suggest that a subgroup of patients with chemotherapy-related leukopenia and fever may benefit from GM–CSF treatment in view of the observed effects on neutrophil count.
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INTRODUCTION

SEVERAL COLONY stimulating factors (CSFs) have been cloned [1–3], which offers the opportunity to test *in vivo* whether CSFs can circumvent chemotherapy-related leukopenia or accelerate bone-marrow restoration after chemotherapy [4–12]. Such an effect might decrease the risk of infections in these patients, especially in those with a granulocyte count below 0.5 × 10^9/l [13, 14].

As well as stimulating the *in vitro* and *in vivo* proliferation of immature myeloid progenitor cells [15, 16], granulocyte–macrophage CSF (GM–CSF) enhances the functional activities of neutrophils and monocytes, such as superoxide production [17–21], phagocytic activity [18, 22–24] and cytokine release [24–26]. The induction of cytokines by GM–CSF may have certain disadvantages during septicaemia, since *in vitro* studies have shown that GM–CSF can increase endotoxin-induced tumour necrosis factor (TNF) release from monocytes [26].

In this double-blind randomised trial we have studied whether GM–CSF can enhance bone-marrow restoration during leukopenia and fever following chemotherapy. In addition we measured tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) levels in serum in 5 patients with gram-positive septicaemia during the first hours of GM–CSF administration.

Correspondence to E. Vellenga.
B. Biesma, E.G.E. de Vries and P.H.B. Willemse are at the Department of Medical Oncology; W.J. Sluiter is at the Department of Endocrinology; P.E. Postmus is at the Department of Pulmonary Medicine; P.C. Limburg is at the Department of Rheumatology; E. Vellenga is at the Department of Hematology, University Hospital, Oostersingel 59, 9713 EZ Groningen, The Netherlands; and A.C. Stern is at the Department of Clinical Research, Sandoz Ltd, Basle, Switzerland.

PATIENTS AND METHODS

Patients

30 consecutive patients, aged 18–75, with a temperature of 38.5°C or more (Terumo digital thermometer for axillary use) and chemotherapy-related leukopenia (white cells 1.0 × 10^9/l or less) were entered. Patients already treated with antibiotics were not eligible. All patients gave informed consent and the study was approved by the medical ethical committee of the University Hospital Groningen. Patients with severe heart, lung, liver (serum total bilirubin 80 μmol/l or more) or kidney impairment (creatinine clearance 30 ml/min or less) were excluded, as were patients with acute myeloid leukaemia or refractory anaemia.

Design and treatment

The study was double-blind and randomised with 15 patients receiving GM–CSF and 15 patients receiving placebo. GM–CSF or placebo was administered as a continuous intravenous infusion for 7 days and was started simultaneously with intravenous antibiotic therapy. Standard antibiotic treatment consisted of tobramycin (1.5 mg/kg three times per day if creatinine clearance was over 100 ml/min) and cefuroxime (1.5 g three times per day), except in patients treated wtih autologous bone-marrow transplantation (ABMT). These patients were treated with netilmycin (2 mg/kg thrice daily) and cefuroxime (1.5 g thrice daily). The duration of antibiotic administration was primarily

based on the temperature of the patient. Antibiotic treatment was not discontinued unless the temperature was normal for at least 2 days.

Recombinant glycosylated mammalian-derived GM–CSF, specific activity of 8 MU/mg protein, was provided by Sandoz/Schering Plough (Basle). The vials contained 0.216 mg glycosylated GM–CSF after reconstitution with the enclosed vehicle. Lyophilised placebo in identical vials was also supplied by Sandoz/Schering Plough. The dosage of GM–CSF was 2.8 μg protein per kg daily by continuous intravenous infusion for 7 days. The daily dose of either active drug or placebo was dissolved in 500 ml glucose 5%. Intravenous administration of GM–CSF or placebo was discontinued if thrombophlebitis developed. The drug was then given subcutaneously twice daily or when infusion possibilities became limited.

Assessments

Blood counts, including differential and reticulocyte counts, were done at entry, daily during GM–CSF or placebo administration, on the 2 days following GM–CSF or placebo administration and twice weekly during the 2 weeks thereafter. Liver and renal functions were assessed at entry, three times during drug administration and once weekly in the following two weeks. At the same times serum levels of cholesterol, sodium, potassium, calcium, total protein and albumin were measured. TNF-α and IL-6 serum levels were retrospectively assayed before, and 1 and 4 h after the start of GM–CSF administration in 5 patients with gram-positive septicaemia. TNF-α (normal value below 5 ng/l) was measured with radioimmunoassay (Medgenix, Belgium). IL-6 (normal below 20 U/ml) was detected with the B9 bioassay [27].

RESULTS

Patients' characteristics and the histology of the primary tumours are shown in Table 1. 5 patients in the GM–CSF group (4 with breast carcinoma and 1 with Burkitt's lymphoma) and 3 patients in the placebo group (2 with breast carcinoma and 1 with non-Hodgkin's lymphoma) had received ablative chemotherapy with ABMT.

All patients had a leucocyte count over 3.0×10^9/l and platelets over 100×10^9/l at the start of the last chemotherapy course. Clinical characteristics are shown in Table 2. In the GM–CSF group positive blood cultures were documented at the start of the study in 47% of the patients compared with 20% in placebo group. Other documented infections at the start of the study were a urinary tract infection with *Escherichia coli* in the GM–CSF group and a gram-positive culture of a phlegmon of the rectovaginal septum in the placebo group. In addition, two clinically documented infections were observed in the GM–CSF group and four in the placebo group.

Table 1. Patients' characteristics

	GM–CSF	Placebo
M/F	9/6	7/8
Median age (yr)	44 (21–74)	52 (18–66)
Diagnosis		
Breast carcinoma	5	6
Small cell lung carcinoma (SCLC)	4	5
Non-small cell lung carcinoma	1	0
Burkitt's lymphoma	1	0
Bladder carcinoma	1	0
Cardiac carcinoma	1	0
Non-seminomatous germ cell carcinoma	1	0
Acute lymphoblastic leukaemia	1	0
Non-Hodgkin's lymphoma	0	3
Neuroblastoma	0	1
Previous radiotherapy	4	1

*Table 2. Clinical characteristics**

	GM–CSF	Placebo
Days since last chemotherapy course	8.5 (3.9) (n = 15)	6.7 (1.4) (n = 15)
Duration of temperature ≥ 38.0°C (days) after start of GM–CSF placebo	2.9 (3.6) (n = 12)	2.4 (2.5) (n = 12)
Infections		
Positive blood culture	7	3
Gram-negative	1	0
Gram-positive	6	3
Other positive cultures		
Urinary tract	1	–
Rectovaginal septum	–	1
Clinically documented infections	2	4
Throat	2	2
Sinus	–	2
Fever of unknown origin	5	7

Mean (S.D.).
*No significant differences between the groups.

Haematological recovery after standard-dose chemotherapy

At the start of the study the mean leucocyte and neutrophil counts were not significantly different between the groups (Table 3). Absolute mean (S.D.) monocyte and eosinophil count at day 0 were 0.1 (0.1) × 10^9/l, and 0.01 (0.02) × 10^9/l (n = 9), respectively, in the GM–CSF group compared with 0.08 (0.09) × 10^9/l and 0.01 (0.02) × 10^9/l (n = 11) in the placebo group (not significant). After 2 days of treatment there was a significantly higher percentage increase in neutrophil count compared with day 0 in the GM–CSF group (4916 [8103]%)

Table 3. Peripheral leucocyte and neutrophil counts in leukopenic patients treated for 7 days with GM–CSF or placebo after standard-dose chemotherapy

	Leucocytes (× 10^9/l)		Neutrophils (× 10^9/l)	
Day	GM–CSF (n = 9)	Placebo (n = 11)	GM–CSF (n = 9)	Placebo (n = 11)
0	0.46 (0.32)	0.64 (0.32)	0.08 (0.10)	0.09 (0.11)
1	0.64 (0.49)	0.67 (0.46)	0.15 (0.24)	0.11 (0.12)
2	1.39 (1.78)	0.95 (0.65)	0.22 (0.45)	0.25 (0.29)
3	2.80 (3.98)	1.74 (1.75)	2.11 (3.70)	1.00 (1.62)
4	4.19 (5.62)	2.83 (3.62)	3.21 (5.00)	0.96 (1.18)
5	6.78 (8.18)	3.72 (3.36)	5.21 (7.00)	2.24 (3.31)
6	8.60 (10.1)	4.83 (4.22)	6.35 (7.90)	3.26 (4.10)
7	11.0 (12.0)	5.61 (4.80)	8.60 (10.1)	3.95 (4.67)

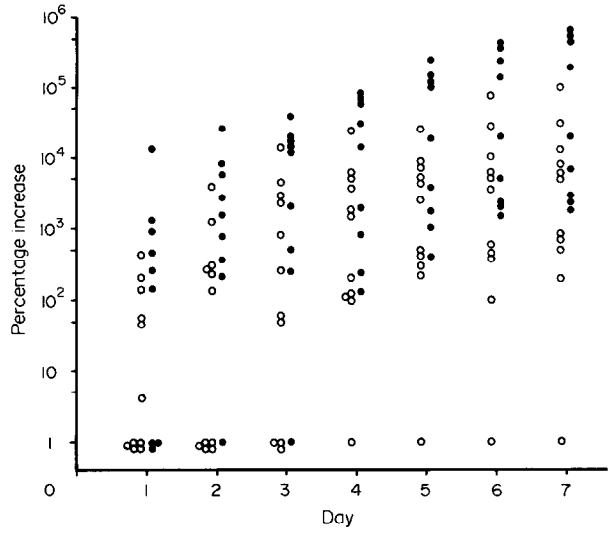

Fig. 1. Percentage increase of neutrophils compared with start of study for GM–CSF (●) and placebo treated patients (○) after standard-dose chemotherapy.

than in the placebo group (513 [1120]%, $P < 0.05$, Wilcoxon rank-sum test) (Fig. 1). However, this difference disappeared after 7 days of treatment (205 447 [264 785]%, vs. 14,649 [29 219]%, respectively). Furthermore, the percentage increase of neutrophils was significantly higher ($P < 0.005$, sign test) during the whole treatment period in the GM–CSF than in the placebo group. Differences in absolute leucocyte and neutrophil counts between the GM–CSF and placebo group were not statistically significant (Table 3).

After 7 days of treatment the absolute numbers of monocytes and eosinophils were, respectively, 1.0 (1.1) × 10^9/l and 0.13 (0.22) × 10^9/l ($n = 9$) in the GM–CSF group compared with 0.75 (0.36) × 10^9/l and 0.01 (0.01) × 10^9/l ($n = 11$) in the placebo group (not significant). A neutrophil count over 0.5 × 10^9/l was reached in the GM–CSF group and the placebo group after 6.3 (3.2) and 6.7 (4.3) days respectively (not significant). 3 patients' counts reached well above the average leucocyte and neutrophil levels. In the GM–CSF group 1 patient had leucocyte counts of 38.0 × 10^9/l (neutrophils 32.0 × 10^9/l) after 7 days of treatment. In the placebo group 2 patients had leucocyte counts of 13.9 and 15.4 × 10^9/l, respectively, (neutrophils 12.8 and 13.0 × 10^9/l) at day 7. All 3 patients demonstrated signs of persisting infections. The recovery of lymphocytes, basophils, platelets (144 [140] × 10^9/l [$n = 9$] in the GM–CSF group and 187 [131] × 10^9/l [$n = 11$] in the placebo group at day 7) and reticulocytes were not affected by GM–CSF administration.

Haematological recovery after ablative chemotherapy and ABMT

Mean leucocyte counts at the start of the study demonstrated no significant differences between the two groups: GM–CSF, 0.06 (0.03) × 10^9/l ($n = 5$) vs. placebo, 0.08 (0.04) × 10^9/l ($n = 3$). Neutrophil counts at entry and after 2 days of treatment were zero in 2 patients in the placebo group and in 3 patients in the GM–CSF group. An additional patient in the GM–CSF group (neutrophil count zero at entry) had a neutrophil count of 0.02 × 10^9/l at day 2. The fifth patient in the GM–CSF group had a neutrophil count of 0.02 and 0.04 × 10^9/l at entry and at day 2, respectively. However, GM–CSF administration in these 2 patients was started 6 days after bone-marrow reinfusion, compared with 3.4 (1.8) days in the other 5 patients. Absolute numbers of leucocytes and neutrophils after 7 days of treatment were 1.5 (0.98) × 10^9/l ($n = 3$) and 0.77 (0.63) × 10^9/l ($n = 3$), respectively, in the GM–CSF group, and 1.1 (1.6) × 10^9/l ($n = 3$) and 0.72 (1.17) × 10^9/l ($n = 3$) in the placebo group (not significant). In addition, GM–CSF did not affect the recovery of eosinophils, monocytes, lymphocytes, basophils, platelets and reticuloctyes.

Clinical results

The number of days with fever after initiation of treatment was not different between both groups: median 1.5 days in both groups (Table 2). Duration of fever in GM–CSF treated patients after standard-dose chemotherapy was 2.7 (3.1) days ($n = 9$) (placebo group 1.8 [2.1] days [$n = 9$]) and after ABMT 3.7 (5.5) days ($n = 3$) (placebo group 4.3 [3.2] days [$n = 3$]). In the GM–CSF group 3 patients were not evaluable for duration of fever because of sudden death in 1 patient on the first day of treatment, and premature discontinuation of GM–CSF on day 5 while fever still persisted in 2 patients. In the placebo group 2 patients were treated with prednisolone from the start of the study and 1 patient's treatment was discontinued prematurely on day 4.

No significant difference was noted in the period of antibiotic administration between GM–CSF and placebo treated patients (10.8 [4.4] vs. 9.6 [4.2] days). Patients not evaluable for duration of fever were also considered not to be evaluable for duration of antibiotic treatment.

Side-effects

There was no significant difference in the frequency (GM–CSF 6/11 patients, placebo 4/12 patients; χ^2 test) and day of onset of thrombophlebitis (GM–CSF 2.8 [1.7] days, placebo 3.9 [1.0] days). In the GM–CSF group the administration of GM–CSF was changed to the subcutaneous route in 2 patients and in the placebo group in 4 patients. In both groups 1 patient received the drug subcutaneously and 2 patients through a central venous catheter since the start of treatment. No other side-effects related to GM–CSF were observed. In none of the patients was excessive weight gain as a sign of capillary leakage noticed. GM–CSF did not affect liver and renal functions or cholesterol levels (GM–CSF, 3.9 [0.9] mmol/l and 3.2 [1.0] mmol/l; placebo, 3.97 [2.1] mmol/l and 4.1 [1.7] mmol/l, at entry and day 7, respectively).

In the GM–CSF group 3 patients did not complete the study. 1 patient, with gram-positive septicaemia, died within 5 h of the start of GM–CSF therapy, probably due to septic shock or cerebral bleeding (permission for necropsy was not obtained). In 1 ABMT patient GM–CSF administration was stopped at day 5 because of persistent high fever (40°C). However, the temperature remained high after cessation of GM–CSF administration. The third patient showed rapidly progressive pulmonary infiltrates on chest X-ray, which correlated with clinical pulmonary deterioration and a fast recovery of leucocytes in the peripheral blood (day 2, 0.08 × 10^9/l; day 5, 2.0 × 10^9/l) during the use of netilmycin, cefuroxime, vancomycin, co-trimoxazol, and amphotericin-B. Therefore, GM–CSF administration was discontinued after 5 days. High-dose prednisolone resulted in clinical stabilisation. In the placebo group progressive jaundice occurred in 1 patient on day 3 but disappeared after discontinuation of clonazepam, ranitidine and placebo. Tumour relapse within a month after the end of the study occurred in 2 patients (1 SCLC, 1 non-Hodgkin's lymphoma) in the placebo group but not in the GM–CSF group.

Table 4. TNF-α and IL-6 serum levels in patients with gram-positive septicaemia treated with intravenous GM–CSF

	Patient*					Hours since start of GM–CSF administration
	1	2	3	4	5	
TNF-α	39	6.9	<5	<5	ND	0
(ng/l)	53	8.7	<5	<5	75	1
	47	ND	37	<5	114	4
IL-6	1000	40	190	320	ND	0
(U/ml)	1500	45	110	370	180	1
	2100	ND	50	60	210	4

*Blood cultures: *Staphylococcus aureus* (patient 1); *Enterococcus faecalis* (patient 2); *Streptococcus mitis* (patients 3, 4); haemolytic *Streptococcus* group C (patient 5).
Normal values: TNF-α < 5 ng/l, IL-6 < 20 U/ml. ND = not done.

Cytokine release

All of 5 tested patients in the GM–CSF group with gram-positive septicaemia had increased IL-6 serum levels at the start of the study (Table 4). In addition, patient 1, who died within 5 h of GM–CSF administration, had an increased TNF-α serum level. Intravenous GM–CSF administration did not affect TNF-α and IL-6 serum levels uniformly during the first hours of GM–CSF administration in these patients, although the IL-6 serum level did increase twofold in patient 1 during this time. The fifth patient (no. 5) had elevated TNF-α and IL-6 serum levels after 1 and 4 h of intravenous GM–CSF administration. However, a sample at the start of GM–CSF administration had not been obtained. No signs of a possible threatening septic shock were observed in this patient. All 5 patients had low monocyte counts (range 0–0.08 × 10^9/l).

DISCUSSION

10–20% of patients treated with cytotoxic drugs will develop infectious complications during one of the chemotherapy courses [28]. In view of this frequency it may be inefficient to treat all patients on chemotherapy with a haematopoietic growth factor to circumvent bone-marrow hypoplasia. However, a CSF may be indicated in patients with an infection, especially since the severity of the infection is determined by the period of leukopenia [14]. Our double-blind study in patients whose treatment with a standard dose of chemotherapy was complicated by fever and leukopenia demonstrated a significantly larger increase in neutrophils during the first days of GM–CSF treatment than in controls. In addition, over the whole treatment period, the increase in neutrophils for the GM–CSF group was significantly larger than that in the controls, which suggests that GM–CSF not only affected the mobilisation of mature cells from the bone marrow but also influenced bone-marrow restoration. In contrast, another pattern occurred in patients treated with GM–CSF within 8 days of ablative chemotherapy and ABMT. No difference in the neutrophil recovery at days 2 and 7 was observed in the GM–CSF compared with the placebo group. The difference in responsiveness between the ABMT and non-ABMT groups can be explained by a lower number of residual haematopoietic progenitor cells in the ABMT group, in which the patients received more intensive chemotherapy. Nissen *et al.* observed similar results in patients with aplastic anaemia treated with GM–CSF [29]. The patients with the most severe degree of aplastic anaemia did not respond to GM–CSF.

The data of patients treated with ablative chemotherapy and ABMT suggest that a short course of GM–CSF may be of little benefit after AMBT. They are also consistent with the time now known to be required, even with GM–CSF treatment, of 10–12 days to achieve a leucocyte response after ABMT [8]. GM–CSF administration may be worthwhile in patients treated with standard-dose chemotherapy, since neutrophil recovery was enhanced. This in turn may shorten the period of antibiotic administration and reduce morbidity and mortality.

Antman *et al.* showed that 2.8 μg/kg GM–CSF per day administered by continuous intravenous infusion is an adequate dose for enhancing leucocyte recovery during chemotherapy-related myelosuppression [4]. Peters *et al.* [30] reported a significant reduction of neutrophil migration to a site of sterile inflammation in patients receiving GM–CSF by continuous infusion, which could be a disadvantage in GM–CSF-treated patients with severe infections. However, additional *in vivo* studies are required to establish the clinical significance of this observation since control of infections has proceeded effectively in patients during GM–CSF treatment. Furthermore, GM–CSF administration may be followed by an immediate transient fall in platelet count [31], which may imply an increased risk of bleeding. Therefore, early platelet transfusion is indicated in severely thrombocytopenic patients during the first hours of GM–CSF administration.

In contrast with the report of Nimer *et al.* [32], we did not observe a significant reduction in serum cholesterol levels during GM–CSF administration. This may be related to the low cholesterol levels in our patients at the start of the study compared with the cholesterol levels in patients with aplastic anaemia studied by Nimer *et al.*

Theoretically, the use of GM–CSF could have clinical disadvantages in patients with septicaemia, since *in vitro* data have shown an increased release of TNF-α in the presence of endotoxin or exotoxin and GM–CSF [26, 33]. This was not seen in our patients. 2 out of 5 patients with gram-positive septicaemia had increased TNF-α serum levels, which did not rise during the first hours of GM–CSF treatment. In addition, IL-6 levels, which were increased in most of the patients at the start of the study, did not rise during the first hours of GM–CSF administration. These *in vivo* data suggest that cytokine release will not further augment during gram-positive septicaemia and GM–CSF administration.

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