Anti-Cancer Drugs 1996, **7**, pp. 392–397

Results of a randomized trial of granulocyte colony-stimulating factor in patients with infection and severe granulocytopenia

Agustin Avilés, Renaldo Guzmán, Edna L García, Alejandra Talavera and José C Díaz-Maqueo
Department of Hematology, Oncology Hospital, National Medical Center, Apartado Postal 7-1220, 06700 México, DF Mexico. Tel: (+52) 5 6 27 69 00.

A study was carried out to investigate the efficacy and toxicity of granulocyte colony-stimulating factor (G-CSF) in the treatment of infection in 119 severely granulocytopenic patients with hematological malignancies after intensive chemotherapy. Patients were assigned randomly to receive either antibiotics alone (ceftazidime, 2 g, i.v., every 8 h + amikacin 7.5 mg/kg, i.v., every 12 h) or the same antimicrobial regimen plus G-CSF (5 μg/kg/day, s.c.). Measurements were clinical improvement, eradication of infection and toxicity. Patients who received antibiotics plus G-CSF had more clinical responses (82 versus 60%), less superinfections (6 versus 20%), less mortality (5 versus 15 patients), less days in hospital (median 10 versus 27) and reduced antibiotic usage compared to patients who received only antibiotics. Hematological recovery (granulocytes > 1.0 × 10^9/l) was also shorter in these patients (12 versus 23 days). Fungal infections occurred only in the group treated with antibiotics alone. Toxicity secondary to G-CSF was absent. We conclude that the addition of G-CSF to broad spectrum antibiotics is useful in selected patients with severe granulocytopenia after intensive chemotherapy and infection, because it may improve the outcome in these patients.

Key words: Granulocyte colony stimulating factor, granulocytopenia, infection, malignant lymphoma, multiple myeloma.

Introduction

Infection continues to be a common cause of morbidity and mortality in granulocytopenic patients undergoing chemotherapy for hematological malignancies. The response rate to antibiotics in many infections now exceeds 80% and response rates of 100% can be obtained with appropriate treatment and accurate microbiological diagnosis.[1] Nevertheless, in some patients with adverse prognostic factors (septicemia, shock, multiorgan failure, previous use of intensive chemotherapy or radiotherapy, fungal infections) the response rate is lower and mortality can be more than 60%.[1] The therapeutic efficacy of antimicrobial agents cannot be explained merely on the basis of the effects of antibiotics on the pathogen involved. Granulocyte recovery remains as the most important prognostic factor.[2–6] If the granulocyte count remains below 0.1 × 10^9/l for more than 7 days the mortality rate can exceed 45%; especially if associated with other pathogens, such as fungi, it became more frequent.[3,7,8] Colony stimulating factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) have been reported to be beneficial in patients with hematological malignancies treated with aggressive chemotherapy who developed severe granulocytopenia and fever; improvement was observed in hematological recovery, reduced mortality, less use of antibiotics and fewer hospitalized days.[8] Also, use of hematopoietic growth factors has been reported to be useful in patients with infection secondary to myelosuppression from chemotherapy.[9–12] For this reason the American Society of Clinical Oncology recently proposed to set up clinical trials to investigate the usefulness of these drugs in this clinical condition.[13]

We began a prospective clinical trial to evaluate the effectiveness and toxicity of G-CSF in patients with microbiologically proven infection and severe granulocytopenia after intensive chemotherapy. The results suggest that G-CSF is useful in this clinical setting.

Material and methods

The study was conducted in the Oncology Hospital, National Medical Center, a tertiary reference center, from January to June 1994. The study was approved by the Ethical Committee of our institution and informed consent was given by all patients. All patients with granulocytopenic infection were

Correspondence to A Avilés

treated with amikacin (7.5 mg/kg, i.v.) every 12 h and ceftazidime (2 g, i.v.) every 8 h. Patients with the following criteria were randomized by sealed envelope to receive in addition G-CSF (5 μg/kg/day, subcutaneously) or not:

(i) diagnosis of hematological malignancy, treated with intensive chemotherapy during induction phase;
(ii) more than 18 years old, with no upper limit:
(iii) fever (> 38.5°C), radiographic and microbiological evidence of bacterial infection;
(iv) HIV negative;
(v) granulocyte count below 0.1×10^9/l, in two consecutive determinations at 12 h interval, secondary to intensive chemotherapy (see below);
(vi) no use of colony-stimulating factors in the last 4 weeks before randomization; and
(vii) no allergy to penicillin or derivatives.

A block system was used to retain balance between treatment arms.

Patients were not included if they showed renal insufficiency (creatinine clearance rate of less than 0.83 ml/min) before treatment.

Patients were eligible for analysis if the following criteria were satisfied: (i) infection microbiologically documented, and (ii) received the antimicrobial agent and/or the G-CSF for at least 3 days according to randomization.

Complete blood count, blood urea nitrogen, serum creatinine and electrolytes, urinalysis and liver function test were measured at the time of study entry, once or twice weekly during the study, and at the end of treatment; patients were assessed for treatment related toxicities. Patients were also examined at least twice weekly for clinical signs or symptoms of adverse effects related to the study drugs. Cultures were obtained from the oropharynx, nasopharynx, perirectal area, stool and blood (by 3) at study entry. If patients remained febrile, culture studies were repeated whenever possible to assess the possibility of bacterial superinfection or fungal infection. If fungal infection was suspected, amphotericin B was added to the treatment and the patient was consider a treatment failure.

Radiographs of the chest were taken at study entry and once weekly until infection resolved. Other investigations were according to the clinical condition of the patient.

The response to therapy was classified as:

- *Improvement:* disappearance of fever for more than 15 days after treatment was stopped with overall clinical improvement and eradication of the infecting organism without modification of the antibiotic therapy.
- *Failure:* persistence of fever or of the infecting organism for more than 3 days, requiring modification of the antibiotic therapy.
- *Non-evaluable:* infection considered unlikely, non-bacterial infection and protocol violations.

Superinfection was defined as a new microbiological or clinically documented infection that occurred either during therapy or within 3 days of the discontinuation of antimicrobial therapy.

A two-tailed Fisher's exact test was used to compared differences in proportion, between groups. Differences between medians were analyzed using the Mann–Whitney *U*-test.

Results

A total of 145 patients entered onto the study. Twenty-six patients were excluded from analysis because infection was considered doubtful or fever could be attributed to a non-infection cause (16 patients), a fungal or viral infection as the only

Table 1. Patient characteristics by treatment group

	Antibiotics alone [*n* (%)]	Antibiotics + G-CSF [*n* (%)]
Number	58 (100)	61 (100)
Median age (range) years	57 (18–83)	60 (23–79)
Men	36 (65)	30 (48)
Women	22 (35)	31 (52)
Underlying disease:		
lymphoma	34 (58)	35 (58)
multiple myeloma	16 (27)	17 (28)
Hodgkin's disease	8 (13)	9 (13)
Central venous catheter	14 (25)	15 (25)

Table 2. Chemotherapy regimens

1. Lymphoma patients
   cyclophosphamide, 3 g/m^2, i.v., on day 1
   etoposide, 1 g/m^2, i.v., on day 7
   epirubicin, 180 mg/m^2, i.v., on day 14

2. Hodgkin's disease patients
   BCNU, 300 mg/m^2, i.v., on day 1
   epirubicin, 120 mg/m^2, i.v., on day 7
   ifosfamide, 5 g/m^2, i.v., on day 7
   etoposide, 1 g/m^2, i.v., on day 14

3. Multiple myeloma patients
   cyclophosphamide 600 mg/m^2, i.v., on day 1
   melphalan, 20 mg/m^2, p.o., daily, days 1–4
   vincristine, 2 mg, i.v., day 1
   dexamethasone, 20 mg/m^2, p.o., daily, days 1–4

documented initial infection (six patients) or an immediate hypersensitivity reaction developed after a single dose of ceftazidime (four patients). The remaining 119 patients were evaluable for both efficacy and toxicity.

Patients in the two treatment arms were similar in age, underlying disease and use of central venous catheters. The time between the last chemotherapy regimen and the initial time of infection was also similar (mean 7 days, range 3–9 days) (Table 1). Table 2 shows the type of chemotherapy given to the patients according to the underlying hematological malignancies. In all cases, the treatment was during the induction phase of previously untreated patients.

Table 3 shows the clinical response to therapy by anatomical site and the hematological recovery. The response rate for bacterial infection in patients receiving antibiotics alone was 60% compared with 82% in the group of patients who received antibiotics plus G-CSF.

Granulocyte recovery to $>0.1 \times 10^9$, $>0.5 \times 10^9$ and $>1.8 \times 10^9$/l was enhanced significantly with the addition of G-CSF to antibiotics (Table 3). No differences were observed in platelet and red blood cell recovery. Also, febrile days and days in hospital were fewer in the group of patients who received G-CSF. The clinical response and hematological recovery were independent of the different hematological malignancies or chemotherapy administered.

Table 4 compares the response to therapy by bacterial pathogens: 21 out of 40 (52%) Gram-negative infections treated with antibiotics alone improved, compared to 35 out of 43 (81%) in the patients treated with antibiotics plus G-CSF. No significant differences were observed in the Gram-positive infections, response was similar (88%) in the group of patients who received antibiotics plus G-CSF compared to 72% in the patients treated with antibiotics alone.

Table 3. Clinical response and hematological recovery

	Antibiotics alone [*n*/*n* (%)]	Antibiotics + G-CSF [*n*/*n* (%)]	*p*
Septicemia	21/39 (53)	34/42 (80)	<0.01
Pulmonary, urinary tract	14/39 (73)	17/19 (89)	NS
Total no. of patients	35/58 (60)	51/61 (82)	<0.01
	58	61	
No. of days to absolute granulocyte count recovery to:			
$>0.1 \times 10^9$/l			
median	11.4	6.0	<0.01
range	8–13	3–9	
$>0.5 \times 10^9$/l			
median	14.8	7.5	<0.01
range	12–16	3–11	
$>1.8 \times 10^9$/l			
median	23.0	11.6	<0.01
range	12–27	8–16	
Days febrile			
median	11.4	6.1	<0.01
range	9–20	4–15	
Hospitalized days			
median	27.0	10.1	<0.01
range	14–33	9–14	
Improvement	35/58 (60)	51/61 (82)	<0.1
Mortality	15.58 (25)	5/61 (8)	<0.01

Table 4. Response according to bacteria

	Antibiotics alone [*n*/*n* (%)]	Antibiotics + G-CSF [*n*/*n* (%)]	*p*
Gram-negative			
Escherichia coli	4/6 (66)	9/9 (100)	
Klebsiella, Enterobacteriaces, Serratio species	8/16 (50)	13/14 (92)	
Pseudomona aeruginosa	6/15 (40)	8/14 (57)	
Proteus species	3/4 (75)	5/6 (83)	
total	21/40 (52)	35/43 (81)	< 0.01
Gram-positive			
Staphylococcus aureus	12/15 (80)	15/16 (93)	
Streptococcus species	2/3 (66)	1/2 (50)	
total	14/18 (77)	16/18 (88)	NS

Table 5. Super infections associated with treatment

	Antibiotics alone [*n* (%)]	Antibiotics + G-CSF [*n* (%)]
Patients	58	61
Patients with superinfections	12 (20)	4 (6)
Bacteria	8	4
Pseudomonas aeruginosa	5	1
Staphylococcus aureus	3	2
Klebsiella pneumonie	0	1
Fungal infections	4	0
disseminated candidiasis	3	
pulmonary aspergillosis	1	

Superinfections

Table 5 shows the type of superinfections associated with each treatment regimen. Patients treated with antibiotics alone showed a high incidence of superinfections (20 versus 6%). Fungal infections were evident only in the patients who were treated with antibiotics alone.

Twenty patients died during the episode of infection. Fifteen cases were on the arm of antibiotics alone and five in the G-CSF and antibiotic therapy group.

Eleven patients died during the initial episode of infection secondary to multiorgan failure. Autopsy was performed in eight cases and infection was the major cause of death. Nine patients died during the superinfection episode and, again, infection in autopsy tissues was the cause of death.

Side effects

Eleven patients developed a transient fall in creatinine clearance; adjustment of the amikacin dose was sufficient to correct this in all cases. Six patients showed mild prolongation of prothrombin time, but no vitamin K was necessary. Five patients developed rash with urticaria after ceftazidime administration. No side effects secondary to G-CSF could be observed.

Discussion

Myelosuppression remains the most important side effect of chemotherapy in the treatment of hematological malignancies. The introduction of more aggressive regimens has been accompanied by more side effects, especially infection. Traditionally, the management of infectious complications, especially in an immunocompromised host, depends on the prompt initiation of therapy with broad-spectrum antibiotics, particularly the combination of an aminoglycoside with a β-lactam.[1,4,7] However, the response to therapy depends on the clinical state of the patient. Patients with severe infection (septicemia, shock, multiorgan failure) have a poor prognosis with a high rate of infection-related death.[1]

Patients who have no recovery of granulocytes $> 0.1 \times 10^9/l$ after more than 7 days have a poor prognosis. Superinfections and infection-related death are common.[3,6] For this reason the outcome of infection remains associated with the speed of granulocyte recovery. A more rapid recovery of granulocytes might lead to an improved outcome from sepsis. The life span of blood cells is generally short; that of granulocytes, which play a leading role in the defense against bacterial infection, is especially short, ranging from several hours to several days.

Granulocytes are differentiated from hematological stem cells and proliferate to maintain host defenses against infection. Hematopoietic growth factors such as G-CSF are involved in the differentiation and proliferation of granulocytes. G-CSF, in particular, specifically promotes granulocytes differentiation and proliferation, and also acts on mature granulocytes to promote activation.[6,8,14]

Hematopoietic growth factors have been shown to shorten the duration of granulocytopenia. Our results show that the use of G-CSF early in the management of infection in severely granulocytopenic patients can improve outcome in these patients. The combination of ceftazidime and amikacin has previously been reported useful in granulocytopenic patients.[1,4,7] The lowest rate of response (60%) in our patients who were treated with antibiotics alone could be attributed to the slow recovery of granulocytes compared with the patients who received G-CSF.

The administration of G-CSF has been shown to be useful in granulocytopenic mice in combination with antibiotics, resulting in improvement in hematological recovery and reduced death from infection.[16] In other clinical studies, the use of G-CSF in granulocytopenia secondary to chemotherapy has improved the cure rate of these patients. Our study confirms that G-CSF shortened the hematological recovery with improvement in granulocyte counts compared with patients who did not receive G-CSF. Also, improvement in clinical response was evident with reduction in the use of antibiotics and hospitalized days. The most important point was that the use of G-CSF reduced the mortality rate compared with patients treated with antibiotics alone in patients with severe infection and poor prognostic factors. The use of G-CSF in patients with infection was not associated with side effects and thus G-CSF can be used safely in this clinical condition. However, the chemotherapy used in our patients was higher than standard regimens in patients with Hodgkin's disease and malignant lymphoma, and the subsequent granulocytopenia tends to be more severe and prolonged. Patients with less severe granulocytopenia probably will not benefit from the use of G-CSF or other hematopoietic growth factors during sepsis, but no randomized studies have been performed to establish this. On the other hand, aggressive chemotherapy is in general use in more curable diseases sensitive to chemotherapy and the number of patients with severe granulocytopenia will probably increase in the near future. For this reason, myelosuppression with lethal infection remains an important risk in patients with cancer who receive aggressive chemotherapy. In such patients the use of G-CSF during infectious episodes can improve the outcome. Further randomized clinical trials will have to be conducted to establish this further.

References

1. Hughes WR, Armstrong D, Bodey GP, *et al.* Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *J Infect Dis* 1990; **161**: 381–96.
2. Bodey GP, Buckley M, Sathe YI, *et al.* Quantitative relationship between circulating leucocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64**: 328–40.
3. Avilés A, Prato CV, Sinco A, *et al.* Evaluación de dos combinaciones de antimicrobianos para el tratamiento de pacientes con neutropenia e infección. *Rev Méd IMSS* 1986; **24**: 349–54.
4. Avilés A, Prato CV, Pizzuto J. Infecciones en pacientes con granulocitopenia. II. Evaluación de dos programas terapéuticos. *Rev Méd IMSS* 1987; **25**: 11–6.
5. Sawyer DW, Donowitz GR, Mandell P. Polymorphonuclear neutrophils, an effective antimicrobial force. *Rev Infect Dis* 1986; **11** (suppl 7): S1532–44.
6. Roilides E, Pizzo P. Modulation of host defense by cytokines. Evolving adjuncts in prevention and treatment of serious infections in immunocompromised host. *Clin Infect Dis* 1993; **15**: 508–24.
7. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. Efficacy and toxicity of a single daily dose of amikacin and cefaperazone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. *Ann Intern Med* 1993; **119**: 584–93.
8. Lischke GJ, Burguess AW. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. *N Engl J Med* 1992; **327**: 28–35 and 99–106.
9. Biesma P, deVries EG, Willemse PH, *et al.* Efficacy and tolerability of recombinant human granulocyte colony stimulating factor in patients with chemotherapy related leukopenia and fever. *Eur J Cancer* 1990; **26**: 932–6.
10. Mayordomo JL, Rivera F, Díaz-Puente MT, *et al.* Decreasing morbidity and cost of treating febrile neutropenia by adding G-CSF or GM-CSF to standard antibiotic therapy.

Proc Am Soc Clin Oncol 1993; **12**: 437 (abstr).
11. Maher D, Lischke JG, Green M, *et al.* Filgastrin in patients with chemotherapy induced febrile neutropenia. A double blind placebo controlled trial. *Ann Intern Med* 1994; **121**: 492–501.
12. Endo S, Inada K, Inonue Y, *et al.* Evaluation of recombinant human granulocyte colony stimulating factor (rhG-CSF) therapy in granulocytopenia patients complicated by sepsis. *Curr Ther Res Opin* 1994; **13**: 233–41.
13. American Society of Clinical Oncology. Recommendations for the use of hematopoietic growth factors. Evidence-base, clinical practice and guidelines. *J Clin Oncol* 1994; **12**: 2471–508.
14. Rose RM. The role of colony-stimulating factors in infectious disease. Current status. Future challenges. *Semin Oncol* 1992; **19**: 415–21.
15. Winston DJ, Ho HG, Bruckner DA, *et al.* Therapy in febrile granulocytopenic patients. *Ann Intern Med* 1991; **115**: 849–59.
16. Matsumoto M, Matsubana A, Yokota T. Effects of combination therapy with recombinant human granulocyte colony-stimulating factor (rG-CSF) and antibiotics in neutropenic mice unresponsive to antibiotic alone. *J Antimicrob Chemother* 1991; **28**: 447–53.

(Received 21 November 1995; received in revised form 13 February 1996; accepted 5 March 1996)