

SHORT REPORT

Tolerance of granulocyte donors towards granulocyte colony-stimulating factor stimulation and of patients towards granulocyte transfusions: results of a multicentre study

J. Bux,¹ U. Cassens,² T. Dielschneider,³ M. Duchscherer,⁴ E. Edel,⁵ H. Eichler,⁶ C. Haas,⁷ R. Moog,⁸ H. Peschke,⁹ C. Peters,¹⁰ I. Ryzhenkov,¹ P. Schlenke,¹¹ H. Ullrich¹² & M. Wiesneth¹³

¹Department of Transfusion Medicine, University of Giessen, Giessen, Germany

²Department of Transfusion Medicine, University of Münster, Münster, Germany

³Department of Transfusion Medicine, University of Hamburg, Hamburg, Germany

⁴Department of Transfusion Medicine, University of Frankfurt, Frankfurt, Germany

⁵Department of Transfusion Medicine, University of Leipzig, Leipzig, Germany

⁶Department of Transfusion Medicine, University of Mannheim, Mannheim, Germany

⁷Department of Transfusion Medicine, University of Marburg, Marburg, Germany

⁸Department of Transfusion Medicine, University of Essen, Essen, Germany

⁹Department of Transfusion Medicine, University of Halle, Halle, Germany

¹⁰St. Anna Kinderspital Wien, Wien, Austria

¹¹Department of Transfusion Medicine, University of Luebeck, Luebeck, Germany

¹²Department of Transfusion Medicine, University of Regensburg, Regensburg, Germany

¹³Department of Transfusion Medicine, University of Ulm, Ulm, Germany

Vox Sanguinis

Data of 507 granulocyte donations from 183 donors were evaluated. No severe granulocyte colony-stimulating factor (G-CSF)-related side-effects were observed. Three donors complained of severe itching following infusion of hydroxyethyl starch (HES). A high proportion (85%) of the donors stated that they would donate granulocytes again. The mean granulocyte yield was 4.3×10^{10} . High-molecular-weight HES resulted in a significantly higher yield compared with low-molecular-weight HES. Mild, but no severe, adverse transfusion reactions were observed in 16% of the recipients. A leucocyte alloimmunization rate of 24% was found. G-CSF stimulation and transfusion of G-CSF-mobilized granulocytes were well tolerated by donors and recipients, respectively.

Key words: granulocyte transfusion, G-CSF, granulocyte apheresis.

Received: 20 August 2003,
revised 15 September 2003,
accepted 27 September 2003

Introduction

As consequence of the use of recombinant granulocyte colony-stimulating factor (G-CSF) in the conditioning of granulocyte donors, new interest has emerged in granulocyte transfusion therapy. As a result, a 2-year multicentre study was undertaken by the German Society of Blood Transfusion and Immunohematology to:

(1) develop a common preparation protocol;

(2) collect adverse effects of G-CSF stimulation and granulocyte apheresis;

(3) follow up stimulated donors, as suggested by ethical considerations [1]; and

(4) document side-effects of G-CSF-mobilized granulocytes in recipients.

Subjects and methods

The study was registered with the German Authorities. Approval was obtained from the institutional review boards, and informed consent of the donors was provided according to the declaration of Helsinki. All family and random donors met the criteria of the German guidelines for blood donations

Correspondence: Juergen Bux, MD, Institute for Clinical Immunology and Transfusion Medicine, Langhansstrasse 7, 35385 Giessen, Germany
E-mail: Juergen.Bux@immunologie.med.uni-giessen.de

and apheresis. G-CSF (Filgrastim or Lenograstim) was administered at a dose of 5 µg/kg body weight, subcutaneously, 8–16 h before apheresis. No additional steroids were used. As a sedimentation agent, 10 ml/kg of regular HES 450/0.7 or of medium-molecular-weight HES 200/0.5 was utilized, but not more than 750 ml of HES was used during a single apheresis. The number of granulocyte donations was limited to four per donor and year. Consecutive daily or alternate-day collections were undertaken. A processed blood volume of ≈ 7 l was recommended. Granulocyte concentrates obtained from ABO- and RhD-compatible donors were irradiated (30 Gy). A leucocyte crossmatch, which comprised at least a lymphocytotoxicity test, was performed prior to undertaking a series of granulocyte transfusions from each donor.

Results and Discussion

A total of 507 granulocyte concentrates collected from 183 donors (male, $n = 138$; female, $n = 45$) were evaluated. The mean donor age was 37 (range 18–65) years. A mean dose of 5.1 µg of G-CSF/kg body weight (range 3.6–10 µg/kg) was administered. G-CSF administration was well tolerated in our

study and side-effects were mild, as shown in Table 1. However, the rate of G-CSF-related side-effects increased from 58% after the first administration to 63% after the fourth administration. Apheresis-related reactions were observed in 14% of the donors. Nine donors complained of mild itching and three donors of severe itching related to HES infusion during apheresis. As the latter side-effect is dose-dependent, this finding supports the recommendation to limit the number of granulocyte donations [2]. Only 13 donors with severe bone pain, headache and itching required medication and 5% would not agree to donate granulocytes again (85% agreed). As, in our study, there could be an intervening period of several days between the four donations, a slight (but not significant) decrease of donor haemoglobin and platelet count was observed. The neutrophil counts increased from $24.2 \times 10^9/l$ after the first G-CSF dose to $34.6 \times 10^9/l$ after the fourth dose, which is not significantly different from the neutrophil counts obtained after daily G-CSF administration [3]. After 4 weeks, the blood counts returned to normal in all donors. The granulocyte concentrates showed a mean volume of 279 ml (range 200–470 ml), a median content of 3.8×10^{10} (0.3 – 14.3×10^{10}) granulocytes and 1.0×10^{11} (0.1 – 5.5×10^{11})

Table 1 Granulocyte colony-stimulating factor (G-CSF)-related side-effects in granulocyte donors

	1st donation ($n = 183$)	2nd donation ($n = 150$)	3rd donation ($n = 116$)	4th donation ($n = 61$)
No complaints	77 (42%)	59 (39%)	51 (44%)	23 (37%)
Bone pain				
Mild	45	36	32	14
Severe	1	5	2	1
Headache				
Mild	35	35	22	12
Severe	3	1	3	0
Fatigue				
Mild	28	29	13	10
Severe	4	5	4	3
Myalgia				
Mild	22	22	17	9
Severe	2	1	0	0
Crawling				
Mild	14	8	9	7
Severe	0	2	0	0
Dizziness				
Mild	11	8	6	3
Severe	2	1	0	0
Itching				
Mild	5	5	4	4
Severe	1	1	3	2
Arrhythmia	5	6	3	2
Chill	5	4	2	0
Skin rash, flush, sweating	4	3	3	3
Other side-effects, complained of by not more than one donor	6	3	4	0

	1st transfusion (n = 77)	2nd transfusion (n = 58)	3rd transfusion (n = 39)	4th transfusion (n = 20)
No side-effects	63 (81%)	49 (84%)	34 (87%)	15 (75%)
Fever	8	5	4	2
Skin rash	4			
Chill	2	1	1	1
Dyspnoea	0	2	0	1
Tachycardia	0	1	0	1

Table 2 Side-effects of granulocyte transfusions in patients

platelets, and a median haematocrit of 0.12 (0.02–0.41). The yield increased from a median of 3.41×10^{10} granulocytes in the first donation to 5.52×10^{10} in the fourth donation, with a significant correlation to the HES preparation used. Standard HES 450/0.7, as a sedimenting agent, resulted in a significantly increased granulocyte yield compared with low-molecular-weight HES 200/0.5 (4.1×10^{10} vs. 3.5×10^{10} , $P = 0.01$), confirming the experience of other investigators [4]. Examination of donors, 2–4 weeks and 2 years after their last donation, revealed no GSF-related chronic side-effects. Adverse reactions of granulocyte transfusions in the patients were rare and mild, as shown in Table 2. This was also observed by others [5,6] and has been attributed to the altered expression of membrane glycoproteins (e.g. a decrease in L-Selectin) of G-CSF-mobilized granulocytes. Of 194 transfusion reports evaluated, only three patients complained of respiratory distress; those patients did not require mechanical ventilation. Two of these patients had received granulocyte transfusions despite a positive lymphocytotoxicity crossmatch. Pulmonary reactions, owing to leucocyte antibodies in the recipient, have also been observed by others [7]. In addition, a positive leucocyte crossmatch was reported to adversely affect granulocyte increments and clinical outcomes [8,9] and has been identified as an adverse element in a meta-analysis of prophylactic granulocyte transfusion studies [10]. On the other hand, five patients with life-threatening infections showed only mild febrile reactions in our study, despite a positive lymphocytotoxicity crossmatch, indicating that leucocyte incompatibility is not necessarily associated with severe transfusion reactions.

The transfusion of an adequate dose of granulocytes has been shown to be significantly associated with the efficacy of granulocyte transfusions [10,11]. In our study, a mean of 10.9×10^8 granulocytes/kg body weight (median of 7.5×10^8 /kg, range: 1.3 – 53×10^8 /kg) were transfused. In a canine model of severe granulocytopenia and experimental *Pseudomonas aeruginosa* septicaemia, a granulocyte dose of 2.0×10^8 /kg was found to be efficacious [12]. Qualitative reviews of the literature indicate that, in adults, a daily dose of $> 1 \times 10^{10}$ granulocytes ($\approx 4 \times 10^{10}$) and, in septic neonates, of $> 1 \times 10^9$ /kg, should be administered [11].

A poststudy examination of 21 patients revealed that five (24%) became alloimmunized, which is similar to the rate in a recently published study [5]. Three of these patients developed human leucocyte antigen (HLA) antibodies and, in the other two patients, granulocyte alloantibodies were specified as anti-HNA-2a (NB1) and anti-HNA-3a (5b). In patients with chronic granulomatous disease or bone marrow failure, alloimmunization rates of 78% have been found [7]. However, in our study, the patients were neutropenic because of chemotherapy or following haematopoietic stem cell transplantation.

References

- 1 Volk EE, Domen RE, Smith ML: An examination of ethical issues raised in the pretreatment of normal volunteer donors with granulocyte colony-stimulating factor. *Arch Pathol Lab Med* 1999; 123:508–513
- 2 Mishler JM, Hester JP, Huestis DW, Rock GA, Strauss RG: Dosage and scheduling regimens for erythrocyte-sedimenting macromolecules. *J Clin Apheresis* 1983; 1:130–143
- 3 Worel N, Kurz M, Peters C, Hoecker P: Serial granulocytapheresis under daily administration of rHuG-CSF: effects on peripheral blood counts, collection efficiency, and yield. *Transfusion* 2001; 41:390–395
- 4 Lee JH, Leitman SF, Klein HG: A controlled comparison of the efficacy of hetastarch and pentastarch in granulocyte collections by centrifugal leukapheresis. *Blood* 1995; 15:4662–4666
- 5 Price TH, Bowden RA, Boeckh M, Bux J, Nelson K, Liles WC, Dale DC: Phase I/II trial of neutrophil transfusions from donors stimulated with G-CSF and dexamethasone for treatment of patients with infections in hematopoietic stem cell transplantation. *Blood* 2000; 95:3302–3309
- 6 Peters C, Minkov M, Matthes-Martin S, Pötschger U, Witt V, Mann G, Höcker P, Worel N, Stary J, Klingebiel T, Gadner H: Leucocyte transfusions from rhG-CSF or prednisolone-stimulated donors for treatment of severe infections in immunocompromised neutropenic patients. *Br J Haematol* 1999; 106:689–696
- 7 Stroncek DF, Leonard K, Eiber G, Malech HL, Gallin JI, Leitman SF: Alloimmunization after granulocyte transfusions. *Transfusion* 1996; 36:1009–1015

- 8 Adkins DR, Goodnough LT, Shenoy S, Brown R, Moellering J, Khoury H, Vij R, DiPersio J: Effect of leukocyte compatibility on neutrophil increment after transfusion of granulocyte colony-stimulating factor-mobilized prophylactic granulocyte transfusions and on clinical outcomes after stem cell transplantation. *Blood* 2000; 95:3605–3612
- 9 Dahlke MB, Keashen M, Alavi JB, Koch PA, Eisenstaedt R: Granulocyte transfusions and outcome of alloimmunized patients with Gram-negative sepsis. *Transfusion* 1982; 22:374–378
- 10 Vamvakas EC, Pineda AA: Determinants of the efficacy of prophylactic granulocyte transfusions: a meta-analysis. *J Clin Apheresis* 1997; 12:74–81
- 11 Vamvakas EC, Pineda AA: Meta-analysis of clinical studies of the efficacy of granulocyte transfusions in the treatment bacterial sepsis. *J Clin Apheresis* 1996; 11:1–9
- 12 Appelbaum FR, Bowles CA, Makuch RW, Deisseroth AB: Granulocyte transfusion therapy of experimental *Pseudomonas* septicemia: study of cell dose and collection technique. *Blood* 1978; 52:323–331