Granulocyte Transfusion Therapy in Childhood

Elif Aktekin¹ · Ali Bay¹ · Mehmet Yılmaz²

Received: 23 April 2016 / Accepted: 13 October 2016 / Published online: 21 October 2016
© Indian Society of Haematology & Transfusion Medicine 2016

Abstract Despite the use of new broad-spectrum anti-bacterial and anti-fungal agents, infections still represent the major cause of morbidity and mortality in patients with prolonged neutropenia after intensive chemotherapy. The aim of this study is to assess the effect and safety of granulocyte transfusions (GTs) for the treatment of severe life-threatening infections in pediatric patients with febrile neutropenia. In this study, 13 pediatric patients with high-risk febrile neutropenia, who received 24 GTs, were included. GTs were well tolerated in all patients. Upon 24 h post-transfusion, neutrophil and platelet counts increased significantly, when compared to the baseline values. The clinical response and hematologic response rates were 69.2 % respectively. In conclusion, GT is safe and effective in controlling life-threatening infections. Furthermore, randomized controlled studies with long-term follow-up are needed to assess the exact role of GT in the outcome of patients with neutropenia.

Keywords Granulocyte transfusion · Childhood malignancy · Neutropenia

Introduction

Infections are serious problems for cancer and bone marrow failure patients in spite of advanced treatment methods. With the advent of granulocyte colony-stimulating factor (G-CSF) to mobilize neutrophils in healthy donors, granulocyte transfusions have been broadly used to prevent and/or treat life-threatening infections in patients with severe febrile neutropenia and/or neutrophil dysfunction [1]. However, there is a lack of strong clinical evidence to support the use of this treatment strategy, particularly in children [2].

In the present study, we describe our experience with usage of granulocyte transfusions at an urban pediatric hematology center.

Patients and Methods

Study Design and Patient Selection

This is a retrospective review of all children with neutropenia or granulocyte dysfunction who received granulocyte transfusions at Gaziantep University Pediatric Hematology Clinic from May 2013 to July 2015. The patient's physician and availability of eligible directed volunteer donors determined the decision and timing of granulocyte transfusions. All patients had severe neutropenia, defined as an ANC <500 cells/mm³, secondary to chemotherapy. One of these patients who was diagnosed with Leucocyte Adhesion Defect Type III had no neutropenia but life threatening infection. Patients with progressive, life threatening and documented infections or sterile cultures with persistent febrile neutropenia (≥ 38 °C) and antimicrobial and anti-fungal failure after >72 h of therapy were eligible for

✉ Elif Aktekin
elifaktekin@yahoo.com

¹ Division of Pediatric Hematology, Department of Pediatrics, Gaziantep University, Gaziantep, Turkey

² Division of Hematology, Department of Internal Medicine, Gaziantep University, Gaziantep, Turkey

analysis. All patients' parents gave their informed consent and the local ethical committee approved the protocol.

Granulocyte Collection and Transfusions

Donor preparation and aphaeresis were performed according to the protocol of Gaziantep Medical School. All donors gave their written informed consent. All of them were healthy and unrelated. Screening blood tests which included blood type, complete blood count, serologic tests for hepatitis B virus, hepatitis C virus, human immunodeficiency virus, cytomegalovirus (CMV), toxoplasma and brucella were studied.

Approved donors were stimulated 16 mg methylprednisolone per oral for three times and 5 µg/kg of granulocyte-colony stimulating factor (G-CSF) subcutaneously twice 12 h before apheresis. Granulocytes were collected via apheresis over a period of 2.5–3.5 h. A granulocyte count was done on the final product to insure that an adequate dose of at $\geq 1 \times 10^{10}$ granulocytes was collected.

The granulocyte collection procedure was performed using a continuous flow apheresis device (Com.Tec., Fresenius® Medical Care). All granulocyte concentrates were irradiated at 25 Gy. The product was transfused within 2 h of collection. All patients were followed with continuous monitoring when transfusing at hospital.

Outcome Measurements

GTs were given daily until the patients had neutrophil counts $>500/\text{mm}^3$, clinical improvement or patients' unavailability. All patients' neutrophil counts were recorded 24-h after each transfusion. Hematological response was defined as neutrophil counts $>500/\text{mm}^3$ and clinical efficacy was defined as improvement of infectious symptoms and vital signs.

Statistical Analysis

Statistical analysis was performed using SPSS 11.5 for Windows. Descriptive statistics for continuous variables were showed as median, standard deviation, minimum and maximum. For categorical variables, frequency dissociations were given by accounting the number of case and percentage values.

Results

13 pediatric patients (7 males and 6 females) received granulocyte transfusions during 24 separate episodes. One of them received 2 and 3 of them received 3 separate courses of GTs. Patient characteristics and underlying diagnoses are summarized in Table 1, respectively.

The concentrates used were minimum 1×10^{10} and maximum 6.4×10^{10} granulocytes for a single transfusion. All patients had neutrophil increments after GT but 4 patients, who had advanced and refractory disease, had no adequate increment. Clinical and hematological response rates were 69.2 %.

The patients with documented infections, 2 (15.3 %) had *Enterococcus faecium*, one (7.6 %) had *Candida parapsilosis*, one (7.6 %) had *Acinetobacter haemolyticus*, 2 (15.3 %) had *E. coli* and one (7.6 %) had *Staphylococcus hominis*. Other patients who were given GTs, had sterile cultures ($n = 6$, 46.1 %).

We did not observe any adverse events related with granulocyte transfusions and well tolerated by the transfused patients.

Discussion

GTs are typically used in the final stage of febrile neutropenia treatment and when any response cannot be taken for other anti-infective agents. Naturally, their effect is very weak for usage in patients diagnosed with leukemia and using myelosuppressive agents at the last stage. Many clinicians emphasize that early initiation of GTs in neutropenic patients with severe infections, who are not responding to proper antimicrobial treatment, appears to be essential [3]. In our study, patients received GTs at median 21.5 ± 14.5 (range 3–57) days after the onset of severe neutropenia and median 12.8 ± 8.8 (range 2–38) days after the emergence of signs of infection. It has been suggested that the efficacy of granulocyte therapy is proportional to transfused granulocyte dose [4]. According to a previous study, a granulocyte transfusion must contain minimum 1×10^{10} neutrophils for an adult patient for an effective GT [5]. In our study, we used median $2.4 \pm 1.4 \times 10^{10}$ (range 1×10^{10} – 6.4×10^{10}) neutrophil contents per transfusion. Patients had median $115.5 \pm 233.3/\text{mm}^3$ (range 0–980) neutrophil counts before transfusions and median $1132.0 \pm 1006.1/\text{mm}^3$ (range 0–3610) neutrophil counts after 24-h transfusion. According to these results, effective doses of granulocytes were used for each transfusion and they support the literature.

Previous studies of granulocyte recipients have documented acute pulmonary transfusion reaction and shortness of breath, dyspnea, hypoxemia, and lung edema [6]. Thus, concern for serious pulmonary complications is a major limiting factor in the routine use of granulocyte transfusions. We didn't observe any adverse events related with granulocyte transfusions.

Due to the retrospective design of our study and small number of patient population, we cannot make yet any

Table 1 Patients' clinical details

Patient	Age (month)	Sex	Underlying disease-risk	Cause of neutropenia	Infectious agent	Culture site	Duration of neutropenia before GT (day)	Duration of infection before GT (day)	Number of GT	Clinical response (day)	Complication of GT
1	129	M	ALL-relaps	Chemotherapy	<i>E. faecium</i>	Blood culture	57	21	1	–	–
2	103	M	ALL-relaps	Chemotherapy	Undetermined	–	55	13	1	10	–
3	42	M	ALL-HRG	Chemotherapy	Undetermined	–	13	21	2	4	–
3'	42	M	ALL-HRG	Chemotherapy	Acinetobacter	Urine culture	10	11	1	2	–
4	174	F	AML-HRG	Chemotherapy	Undetermined	–	15	3	2	2	–
5	72	M	ALL-HRG	Chemotherapy	<i>C. parapsilosis</i>	Blood culture	10	16	2	1	–
6	197	F	AML-HRG	Chemotherapy	Undetermined	–	15	4	1	1	–
6'	197	F	AML-HRG	Chemotherapy	Undetermined	–	15	2	2	1	–
6''	197	F	AML-HRG	Chemotherapy	Undetermined	–	7	21	1	1	–
7	57	F	ALL-MRG	Chemotherapy	<i>E. coli</i>	Blood culture	25	6	1	1	–
8	59	M	ALL-HRG	Chemotherapy	Undetermined	–	31	8	1	1	–
9	40	F	ALL-MRG	Chemotherapy	<i>E. faecium</i>	Blood culture	28	6	1	1	–
10	120	M	ALL-HRG	Chemotherapy	Undetermined	–	27	13	1	–	–
11	169	M	ALL-relaps	Chemotherapy	<i>Staf. hominis</i>	Blood culture	37	15	1	–	–
11'	169	M	ALL-relaps	Chemotherapy	Undetermined	–	25	38	1	–	–
11''	169	M	ALL-relaps	Chemotherapy	Undetermined	–	12	11	1	–	–
12	112	F	LAD	–	<i>E. coli</i>	Wound culture	–	18	3	–	–
13	72	F	AML-HRG	Chemotherapy	Undetermined	–	16	15	1	1	–

M, Male; F, Female; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; MRG, median risk group; HRG, high risk group; GT, granulocyte transfusion; ', second granulocyte transfusion course; '', third granulocyte transfusion course

speculations regarding whether the use of granulocyte transfusions with antimicrobial therapy is superior to the use of antimicrobials alone as we do not have a comparison group to hold against our study population. Randomized clinical trial is necessary to evaluate safety and whether the GT is superior to antimicrobial-only therapy. We believe that using granulocyte transfusions as early as to patients, who are treated for severe life-threatening infections in pediatric patients with febrile neutropenia, seems beneficial for recovering from the infections.

Compliance with Ethical Standards

Conflict of interest Elif Aktekin, Ali Bay and Mehmet Yılmaz declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Cugno C, Deola S, Filippini P et al (2015) Granulocyte transfusions in children and adults with hematological malignancies: benefits and controversies. *J Transl Med* 13(1):362. doi:[10.1186/s12967-015-0724-5](https://doi.org/10.1186/s12967-015-0724-5)
2. Ozturkmen S, Altuntas F, Olcay L (2013) Granulocyte transfusion therapy in paediatric patients with severe neutropenic infection. *Transfus Apher Sci* 48:381–385
3. Atay D, Ozturk G, Akcay A et al (2011) Effect and safety of granulocyte transfusions in pediatric patients with febrile neutropenia or defective granulocyte functions. *J Pediatr Hematol Oncol* 33:e220–e225
4. Stanworth SJ, Massey E, Hyde C (2005) Granulocyte transfusions for treating infections in patients with neutropenia or neutrophil dysfunction. *Cochrane Database Syst Rev* CD005339. doi:[10.1002/14651858.CD005339](https://doi.org/10.1002/14651858.CD005339)
5. Price TH (2006) Granulocyte transfusion therapy. *J Clin Apher* 21:65–71
6. Cesaro S, Chinello P, De Silvestro G et al (2003) Granulocyte transfusions from G-CSF-stimulated donors for the treatment of severe infections in neutropenic pediatric patients with onco-hematological diseases. *Support Care Cancer* 11:101–106