ORIGINAL ARTICLE

Clinical Experience of Granulocyte Transfusion Therapy in Pediatric Patients for Management of Neutropenia-related Infections in a Tertiary Care Center in India

Sunil Bhat[1], Sohini Chakraborty[2], Pooja Mallya[3], Shobha Badiger[4], Prathip Kumar[5]

Abstract

Introduction: In neutropenic patients bacterial and fungal infections are a major cause of morbidity and mortality, especially in hematological malignancies and post-hematopoietic stem cell transplantation. We present here a single institution experience with the use of granulocyte transfusions in children with severe neutropenic sepsis.

Material and methods: This is a retrospective analysis of 48 children who received a total of 120 granulocyte transfusions following mobilization with colony-stimulating growth factor (G-CSF) and dexamethasone.

Results: Favorable response was seen in 41.6% of the children without any major adverse effects in donor or recipient.

Conclusion and clinical significance: Granulocyte transfusions hence may be a useful adjunct to antimicrobials and growth factors in neutropenic sepsis refractory to conventional antimicrobials.

Keywords: Granulocyte transfusion, Infections, India, Neutropenia, Pediatric patients.

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Background

Bacterial and fungal infections are a major cause of significant mortality and morbidity in neutropenic patients.[1] This is seen commonly in patients after intensive chemotherapy for hematological malignancies or after hematopoietic stem cell transplantation. Unrestricted antimicrobial use has further worsened the situation due to the development of drug resistance all over India.[2] In a surveillance study in pediatric oncology patients from a cancer center in India in Mumbai, a prevalence of community-acquired multidrug-resistant organism colonization especially due to carbapenem-resistant *Enterobacteriaceae* was as high as 60% and was associated with a mortality of 58–70%.[3] With the increase in incidence of drug resistance, many of these infections do not respond to treatment with appropriate antimicrobial agents. Granulocyte transfusions can help restore neutrophil counts and thus theoretically aid in the resolution of infection in such patients. Studies have shown granulocyte transfusion therapy to be a useful supportive therapy in this scenario.[4–6] We conducted the present study to determine the clinical course and outcome of neutropenic patients with infections who received granulocyte transfusions at our center.

Materials and Methods

Retrospective observational analysis of all pediatric patients up to 18 years of age receiving granulocyte transfusions in our hospital between July 2015 and December 2016.

Donors

All selected candidates were voluntary donors who were blood group compatible with the recipient and had no significant comorbidities. Routine pretransfusion tests were performed on all donors including a complete blood count and viral screen. Multiparous women were avoided as donors in view of the risk of alloimmunization. After obtaining informed consent, subcutaneous 10 µg/kg colony stimulating growth factor (G-CSF) along with 8 mg oral dexamethasone was administered 8–12 hours before granulocyte collection in all donors.

Granulocyte Collection and Transfusion

All granulocyte concentrates were collected using COBE Spectra cell separator without the use of hydroxyethyl starch. Peripheral venipuncture was used as vascular access in all donors. All granulocyte concentrates were irradiated with 25 Gy and transfused to the patient at a dose of 10 mL/kg within 6 hours of collection with appropriate premedications.

Patients

Patients with neutropenia [absolute neutrophil count (ANC) < 500/µL] and severe, progressive infections not responding to use of appropriate antimicrobials and G-CSF were eligible for inclusion.

[1–4]Department of Pediatric Hematology, Narayana Health City, Oncology and Bone Marrow Transplant, Bengaluru, Karnataka, India

[5]Department of Transfusion Medicine, Narayana Health City, Bengaluru, Karnataka, India

Corresponding Author: Sunil Bhat, Department of Pediatric Hematology, Narayana Health City, Oncology and Bone Marrow Transplant, Bengaluru, Karnataka, India, Phone: +91 9538965968, e-mail: sunilbhat_9@hotmail.com

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Granulocyte transfusions were continued daily until one of the following: Increase of neutrophil count to >500/μL, resolution of infection, non-availability of donors, or severe transfusion reactions. Absence of fever for >48 hours, improvement in clinical symptoms that were present at onset, repeat negative cultures in patients with previous positive cultures, and radiological improvement were considered as resolution of infection.

The response to granulocyte transfusion was considered "favorable" if the patient survived the infection episode and there was resolution of infection as defined above. In case of mortality or progression of the clinical symptoms and signs, response was considered "unfavorable".

Statistical analysis was performed with SPSS 10.0 using appropriate statistical tests.

Results

Forty-eight patients (males = 25 and females = 23) were included in the study who received a total of 120 granulocyte transfusions. The median age of the patients was 108 months (range 5–192). The diagnoses of patients included acute myeloid leukemia (n = 8), acute lymphoblastic leukemia (n = 17), chronic myeloid leukemia (n = 2), idiopathic severe aplastic anemia (n = 8), Fanconi anemia (n = 3), myelodysplastic syndrome (n = 1), and thalassemia (n = 8). Twenty-six of these 48 patients were in the neutropenic phase post-hematopoietic stem cell transplantation. The median duration of neutropenia before granulocyte transfusion was 11 days (range 2–34), and the median duration of antimicrobial therapy and G-CSF before the initiation of granulocyte transfusions were 10 days (range 3–20) and 9 days (range 2–10), respectively (Table 1). Donor characteristics are shown in Table 2. All donors tolerated the procedure well with no major adverse effect. The most common side effect seen was myalgia.

The sites of infection and isolated organisms are shown in Table 3. Sixteen out of 48 (33.3%) patients had localized infections while remaining 32 (66.7%) had sepsis.

Patients received a median of 2.85 granulocyte transfusions (range 1–8) with a median cell dose of 2.7×10^{10}/L granulocytes (shown in Table 4). Most transfusions were well tolerated except for the occurrence of transfusion-associated acute lung injury (TRALI) in one patient. In 30/48 (62.5%) patients, granulocyte therapy had to be stopped early due to unavailability of voluntary donors.

Favorable response was seen in 20 patients (41.6%), whereas unfavorable response was seen in 28 patients (58.4%). Twelve out of 32 patients with sepsis (37.5%) and 8/11 patients with pneumonia (72%) had favorable response. Nine out of 23 (39%) patients with gram-negative etiology, 1/1 (100%) with fungal etiology, 1/2 (50%) with viral etiology, and 8/20 (40%) patients with unidentified etiology showed favorable response.

Table 1: Baseline characteristics of patients for whom granulocyte infusions were used

Characteristics of patients	*Number*	*Percentage (%)*	*Median*	*Range*
No. of patients	48			
Sex				
Male	25	52.1		
Female	23	47.9		
Age			108	5–192 months
Primary diseases				
AML	8/48			
ALL	17/48			
CML lymphoid blast crisis	2/48			
Extra osseous Ewing's sarcoma	1/48			
Myelodysplastic syndrome	1/48			
Aplastic anemia	8/48			
Fanconi anemia	3/48			
Thalassemia	8/48			
Duration of neutropenia before granulocyte			11 days	2–34 days
Duration of antimicrobials before granulocytes			10 days	3–20 days
Duration of G-CSF before granulocyte			9 days	2–10 days

AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; CML: Chronic myeloid leukemia; G-CSF: Colony-stimulating growth factor

Table 2: Granulocyte donor characteristics

Donor characteristics	*Number*	*Median*	*Mean*
Number of donors	120		
Donor pre-leukapheresis WBC count		31.9×10^9/L	
Donor granulocyte yield			8.9×10^{10}/L
Severe adverse effect in donor	0/120		

Discussion

Granulocytes can theoretically be an effective adjunct in the management of neutropenic patients with severe life-threatening infections. There have been multiple studies in the past with conflicting results.

Colony-stimulating growth factor is used to mobilize granulocytes into peripheral blood from bone marrow for apheresis. In healthy donors, the response to G-CSF is dose-dependent with an increase in the neutrophil count within 2 hours, peaking at 12 hours. Study of neutrophil function after G-CSF administration has also shown increased migration to sites of inflammation/infection[7] that probably helps in controlling the infection. Several studies have shown the benefit of use of G-CSF plus dexamethasone-based mobilization regimen in healthy donors which leads to a higher granulocyte yield in comparison to G-CSF or dexamethasone alone.[8] Priming with G-CSF plus dexamethasone, besides increasing the neutrophil yield, also upregulates the expression of genes for multiple toll-like receptors (TLR-2, TLR-4, TLR-5, and TLR-8).[9] This leads to a heightened response against microbes causing donor cells to produce large quantities of IL-8, which in turn increases the antimicrobial activity of the transfused donor granulocytes.[9] In this study, both dexamethasone and G-CSF were used for granulocyte mobilization.

Granulocyte transfusions have been mainly used in neutropenic patients with severe, progressive infections that fail to respond to appropriate antimicrobial agents within approximately 48

Table 3: Pattern of infections in the patients getting granulocyte infusions

Infections	*Number*	*Percentage (%)*
Localized infection	16/48	33.3
Sepsis	32/48	66.7
Sites of localized infection		
Pneumonia	11	
Typhlitis	3	
Orbital cellulitis	1	
Encephalitis	1	
Infective etiology known	28/48	58.3
Causative organisms		
MDR *E. coli*	8/30	
Pseudomonas	3/30	
MDR *Klebsiella pneumoniae*	7/30	
MDR *Acinetobacter*	4/30	
Stenotrophomonas maltophilia	1/30	
Viral (CMV/adenovirus)	2/30	
Gram-positive sepsis	2/30	
Candida tropicalis	1/30	

Table 4: Cell doses received and recovery pattern in patients

Transfusions	*Number*	*Median*	*Range*
Granulocyte transfusions received		2.85	1–8
Cell dose		2.7×10^{10}/L	
Days to neutrophil recovery		5	3–17
Adverse effects	1/48		

hours.[10,11] There is controversy regarding cell dose to be used during granulocyte therapy and its relation with efficacy. The minimum cell dose required for a measurable neutrophil increment is $2–3 \times 10^{10}$ and transfusions are usually continued until the ANC increases above 500/μL and the infection resolves.[10,11] The median cell dose used in our patients was 2.7×10^{10}/kg which were similar to the above studies. In the recently concluded RING study, it was found that patients who received a higher dose of granulocytes ($>0.6 \times 10^9$/kg) had significantly better survival at 42 days in comparison to those receiving a lower dose.[12] In another study, it has been observed that patients receiving median doses of $1.5–3.0 \times 10^8$ granulocytes/kg had reduced infection-related mortality.[13] Also, Garg et al.[14] demonstrated in their study that doses $>10 \times 10^8$/kg though associated with a higher total leucocyte count (TLC) increment at 6 hours post-infusion had no significant impact on survival at 30 days.

Several studies have proved the safety and the feasibility of granulocyte transfusions in patients with treatment-refractory severe bacterial sepsis along with the reduction in death rate.[15,16] Atay et al. analyzed 35 pediatric patients with high-risk febrile neutropenia or defective granulocyte functions who received 111 granulocyte transfusions. The infection-related survival was 82.4% while overall survival (OS) was 77% at day 30.[17] Garg et al.[14] also analyzed the efficacy of granulocyte therapy in combating life-threatening infections in patients of hematological disorders/recipients of hematopoietic stem cell transplant (HSCT) with severe neutropenia. A total of 143 granulocyte transfusions in 60 patients were included. Resolution of index infection was seen in 68.2%, and the 30-days OS was 67.7%. Zhou et al. also retrospectively analyzed the clinical outcomes of 47 patients among whom 72.3% had resolution of infections. In addition, they found in their study that granulocyte therapy benefited the patients who suffered from pulmonary bacterial infections (80%) more as compared with the bloodstream infection group (58.3%) and skin or mucous infection group (20%).[18] In our study, also 72% patients of pneumonia responded to granulocyte transfusions in comparison to 37.5% with sepsis.

Studies have shown definite benefit in patients with refractory fungal and gram-negative infections; however, no effect was demonstrated in patients with infections with gram-positive organisms. This was possibly due to the abnormal early uptake and persistent retention of neutrophils at sites of gram-negative infections while uptake is normal at sites of gram-positive infections.[8] In our center, gram-negative organisms were the leading cause of sepsis and hence comparison between response to gram-negative and gram-positive organisms could not be assessed in our study.

Also, time of initiation of granulocyte transfusions have shown to play an essential role in determining their efficacy. Survival chances are superior when transfusion is performed early in the septic crisis particularly prior to the onset of end-organ damage leading to multisystem failure. Sachs et al. reported a 92.6% overall response rate to early granulocyte transfusions (median infection period 6 days range 3–18 days) and a favorable toxicity profile.[5] In another study by Uppuluri et al., the early institution of granulocytes within 48 hours of a septic episode led to a statistically significant improvement in survival from 41% to 54%.[2] Garg et al. in their study also found that OS was significantly higher in patients who received granulocyte transfusion (GTX) within 7 days of neutropenic sepsis ($p = 0.01$).[14] In our present study, due to financial constraints and unavailability of donors, granulocyte transfusions could not be initiated early within 48 hours in most of the subjects probably leading to an inferior response rate in comparison to other studies.

The number of granulocyte transfusions given in succession is also an important determinant of efficacy. Seidel et al.[16] reported that daily granulocyte transfusions given for at least 5 days and containing a minimum of 3×10^8/kg neutrophils per concentrate, was able to generate a stable ANC increment, shorten the duration of neutropenia, and support the control of infections in neutropenic patients with high-risk infections. In our study, due to non-availability of donors, granulocyte transfusions had to be stopped before recovery of neutropenia in 62.5% patients which might have impacted the efficacy.

Adverse reactions were rare in recipients; the most common being fever with chills and rigor.[9] Transfusion-associated acute lung injury presenting as pulmonary edema and respiratory failure and transmission of cytomegalovirus infections have also been documented with granulocyte transfusions.

Conclusion

Granulocyte transfusions are a generally safe adjunct in the management of severe neutropenia-related infections unresponsive to conventional modalities of treatment. Studies with larger numbers are required to corroborate the findings of these studies preferably in a prospective fashion.

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