Granulocyte Transfusion Therapy: Institutional Experience of Benefit in Cancer Patients with Prolonged Neutropenic Sepsis—A Retrospective Study

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Abstract

Introduction Patients undergoing intensive chemotherapy for hematological malignancy and stem cell transplantation are at increased risk of neutropenia.

Neutropenia is among the frequent side effects of intensive treatments, and when absolute neutrophil count (ANC) falls $< 500/\mu L$, the risk of microbial and fungal infection increases significantly.

As neutropenia is the main cause of these infections, transfusion of granulocyte immediately as a replacement is a life-saving therapeutic option to support these patients by restoring neutrophil counts and aiding in the resolution of infection.

Objective The present study is a retrospective single institutional analysis of granulocyte transfusion therapy in children and young adults with cancer who received treatment with GT during prolonged and profound life threatening neutropenia.

Materials and Methods This study was a retrospective analysis of 66 granulocyte transfusions in 36 patients of hematological and solid malignancy with severe and prolonged neutropenia in the department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences Indore, between September 2019 and March 2022.

Donors were either patients' relatives or voluntary donors without comorbidities.

All granulocyte concentrates were collected by centrifugation leukapheresis and irradiated with 2500 centigray and immediately transfused in full, to the patient over 60 ot 120 minutes with appropriate premedication.

Results A total of 36 patients (M:F, 19:17) with a median age of 16 years (2–43) received 66 granulocyte transfusions. The diagnosis of patients included acute myelogenous leukemia ($n = 17$), B cell acute lymphoblastic leukemia ($n = 10$), non-Hodgkin lymphoma ($n = 3$), Ewing's sarcoma ($n = 2$), neuroblastoma ($n = 1$), malignant melanoma ($n = 1$), aplastic anemia ($n = 1$), osteosarcoma ($n = 1$). All had severe neutropenia with absolute neutrophil count $< 0.5 \times 10^9/L$. The median duration of

Keywords
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- neutropenia

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severe neutropenia was 16 days. Patients received a median cell dose of granulocytes 2.9×10^{10}/L. A favorable response was seen in 28 (78%) patients, whereas an unfavorable response was seen in 8 patients (23%).

Conclusion A granulocyte therapy was effective in many critically sick patients with prolonged and profound neutropenia. Granulocyte transfusions may be more beneficial in selected patients where it provides more time to overcome refractory infections with broad-spectrum antibiotics. Granulocyte transfusion are at best a "bridge" that gives time to marrow recovery. The challenges to using GT are clinical, finding patients who may get benefitted, and logistical, selection of donors and harvest technique. Randomized trials with large numbers of patients are required to prepare guidelines for granulocyte use.

Introduction

Patients received aggressive chemotherapy for hematological malignancy and stem cell transplantation are at higher risk of neutropenia.

Bacteria, viruses, and fungi are the main complication-producing agents in most patients with profound and prolonged treatment related to neutropenia despite newer antimicrobials and antifungals.

Neutropenia is among the common side effects of intensive treatments, and when absolute neutrophil count (ANC) falls < 500/µL (Grade IV neutropenia), the risk of microbial and fungal infection increases significantly.

As of now, bacterial and fungal infections such as *Aspergillus* and *Fusarium* in patients with neutropenia have increased and eventually morbidity and mortality rates.[1]

Improvement in the overall general and intensified care in oncology units with the use of newer and effective broad-spectrum antimicrobial and antifungal drugs resulted in significantly better survival.

Irrational prescription of higher antimicrobial and antifungal without checking the sensitivity has led to the development of resistance to these drugs across India and due to this, dreaded infections do not respond as needed.[2]

As neutropenia is the main cause of these infections, transfusion of granulocyte immediately as a replacement is a life-saving therapeutic option to support these patients by restoring neutrophil counts and aiding in the resolution of infection.

Granulocyte transfusion (GT) therapy was conceptualized in the 1960s, and many studies have shown that it is a useful supportive therapy in the case of neutropenia.[3–6]

Granulocytes transfusion used for prophylactic therapy with antimicrobials in patients who received intensive chemotherapy and developed severe neutropenia.[5,7–9]

The present study was a retrospective single institutional analysis of granulocyte transfusion therapy in children and young adults with cancer who received treatment with GT during prolonged and profound life-threatening neutropenia.

Materials and Methods

This study was a retrospective analysis of all patients who received granulocyte transfusions between September 2019 and March 2022 in the Department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences Indore, India.

Granulocyte transfusion (GT) therapy was prescribed in all patients with (1) absolute neutrophil count (ANC) < 500 cells/µL, (2) evidence of bacterial or fungal infection (i.e., clinical presentation, positive cultures, biopsy, or radiological evidence), and (3) lack of response to the recently introduced antimicrobials for 48 hours.

After granulocyte transfusions, we monitored ANC until recovery to > 500/µL. No fever in more than 48 hours, symptomatic relief, and negative cultures with radiological absence of infection were considered as a response. A tandem GT was given to nonresponders.

Donors were either patients' relatives or voluntary donors without comorbidities and blood group incompatibility with the patient. After informed consent, screened donors received subcutaneous colony-stimulating growth factor (G-CSF) 10 µg/kg with injection dexamethasone 8 mg and were taken for granulocyte harvest after 10 to 12 hours via peripheral vascular access by centrifugation leukapheresis using the Fresenius COM TEC system. All harvest volume was irradiation with 2500 centigray and transfused to the patient over 60 to 120 minutes after appropriate premedication.

Statistical Analysis

The data were collected in an Excel sheet and statistical analysis was performed using SPSS, version 23.0. Considering the nature of the study, no formal sample size was employed. Categorical variables are presented as numbers and percentages, whereas continuous variables are expressed as median and range.

Ethics

This study was conducted in accordance with the ethical principles that are consistent with the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practices, and the applicable legislation on non-interventional studies. The study protocol was approved by the institutional ethics committee (IEC no. SAIMS/IEC/2022/11). Informed consent was waivered due to the retrospective nature of the study.

Table 1 Clinical characteristics of patients received granulocyte transfusion therapy

Characteristics of patients	
Number of patients	36
Age (y), median. ange	16 (2–43)
Sex	
Male	19 (53%)
Female	17 (47%)
Underlying disease, *n*	
Acute myelogenous leukemia	17
B-cell acute lymphoblastic leukemia	10
Non-Hodgkin lymphoma	3
Ewing's sarcoma	2
Neuroblastoma	1
Aplastic anemia	1
Malignant melanoma	1
Osteosarcoma	1
Severe neutropenia (ANC $< 0.5 \times 10^9$/μL), *n*	36/36
Duration of neutropenia, days, median (range)	16 (7–24)
G-CSF treatment used before granulocyte therapy	36/36
Systemic treatment with antimicrobial before granulocyte, *n*	36/36
Systemic treatment with antifungal before granulocyte, *n*	36/36
Granulocyte cell dose received, median (range), *n*	2.9×10^{10}/L (2.0×10^{10}/L–4.8×10^{10}/L)
Days to neutrophil recovery, median (range) *n*	9 (3–19)
Adverse effect	1/66

Results

A total of 36 patients (M:F, 19:17) with a median age of 16 years (2–43) received 66 granulocyte transfusions. The disease-wise distribution were acute myelogenous leukemia ($n = 17$), B cell acute lymphoblastic leukemia ($n = 10$), non-Hodgkin lymphoma ($n = 3$), Ewing's sarcoma ($n = 2$), neuroblastoma ($n = 1$), malignant melanoma ($n = 1$), aplastic anemia ($n = 1$), osteosarcoma ($n = 1$). All had severe neutropenia with absolute neutrophil count $< 0.5 \times 10^9$/L. The median duration of severe neutropenia was 16 days (7–24 days). Granulocyte transfusion therapy was prescribed in patients because of persistent neutropenic fever with pneumonia ($n = 18$), soft tissue infections ($n = 8$), neutropenic enterocolitis ($n = 7$), and deterioration in condition despite granulocyte colony-stimulating factor (G-CSF), broad-spectrum antimicrobial therapy and antifungal therapy. GT was given until ANC $> 0.5 \times 10^9$/L. Patients received a median cell dose of granulocytes 2.9×10^{10}/L (range 2.0×10^{10}/L–4.8×10^{10}/L). A favorable response was seen in 28 (78%) patients in terms of early recovery from neutropenia and resolution of infections. The median time to neutrophil count recovery was 9 days (3–19 days), whereas 8 patients (23%) showed poor response, who succumbed to infections. GT were tolerated by all patients except for transfusion-associated acute lung injury (TRALI) in one patient who succumbed despite all intensive care in the hospital. The clinical characteristics of patients who received granulocyte transfusion therapy are shown in ►**Table 1**.

In all 36 patients, post chemotherapy neutropenia was developed, including one post autologous stem cell transplantation. Microbiologically documented infections were seen in 35 patients (97%). Nine patients developed invasive fungal infections and 29 bacterial infections. The infection profile and culture positivity are shown in ►**Table 2**.

All patients received ongoing antimicrobial and systemic antifungal therapy before and during GT treatment. All 66 donors tolerated apheresis well with no adverse effects.

Table 2 Infection profile/cultures in patients

Infection agent	Number of positive cultures
Acinetobacter	1
Klebsiella	17
Pseudomonas	7
Escherichia coli	1
MRSA	3
Candida, mucormycosis	9
Total	38

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 3 Granulocyte donor characteristics

Donor characteristic	Number	Median
Number of donors	66	
Donor pre leukapheresis WBC counts, median (range)		3.17×10^{10}/L (2.19×10^{10}/L–4.49×10^{10}/L)
Adverse effects in donor	0/66	

Abbreviation: WBC, white blood cell.

Median pre leukapheresis WBC counts were 3.17×10^{10}/L (2.19×10^{10}/L– 4.49×10^{10} /L). Granulocyte donor characteristics are shown in ►**Table 3**.

Discussion

Transfusion of granulocytes is an efficacious therapy to fight severe life-threatening bacterial and fungal infections in patients with neutropenia.

Donor injection of colony-stimulating growth factor (G-CSF) with dexamethasone mobilizes granulocytes into the peripheral blood from the marrow, increasing the granulocyte count in 2 to 12 hours.[10] Collection of up to 5 to 10×10^{10}/L granulocytes in one session became possible.[11–13]

Large granulocyte doses raise ANC in patients with neutropenia.[14]

After G-CSF administration, increased neutrophils accumulate at the location of inflammation or infection and help in getting rid of infection.[15]

Lee et al[16] reported G-CSF with dexamethasone was better as compared with dexamethasone alone in mobilizing granulocyte from the bone marrow to peripheral blood to increase harvest volume.

Drewnian et al[17] described that due to upregulation of Toll-like receptors after G-CSF and dexamethasone, donor cells secrete IL-8, which helps in controlling microbial infections.

Progressive infection in neutropenic patients not responding to antimicrobial and antifungal within 48 hours, granulocyte transfusions have been recommended to raise ANC promptly to faster recovery. The therapeutic dose of granulocyte and its efficacy is still controversial. Next, 2–3×10^{10}/kg is the minimum granulocyte dose needed to increase ANC and transfusions are given until the absolute neutrophil counts become more than 500/µL and/or until the resolution of infection.[18,19]

The Resolving Infection in Neutropenia with Granulocytes (RING) trial[20] concluded that patients who received granulocytes dose $> 0.6 \times 10^9$/kg reported improved survival at 42 days as compared with patients who received a dose $< 0.6 \times 10^9$/kg. The median granulocyte dose received by our patients was 2.9×10^{10}/kg equivalent to the above studies.

Nikolajeva et al[21] reported a decrease infection-associated death in patients who received a median cell count of 1.5 to 3.0×10^8 granulocytes/kg.

Garg et al[22] reported that an increase in the total leucocyte count 6 hours after a high dose of 10×10^8/kg of GT did not affect the survival at 30 days.

Grigull et al[7] and Seidel et al[23] reported that granulocyte transfusion is feasible and safe in controlling the treatment of refractory bacterial infection and decreasing mortality.

Atay et al[24] analyzed 35 pediatric patients who had 111 granulocyte transfusions in view of the increased risk of neutropenia, reported 82.4% infection-related survival of 82.4% and overall survival (OS) of 77% at day 30.

Garg et al[22] and Zhou et al[25] showed that granulocyte therapy is useful in managing severe infections due to neutropenia in patients with hematological disorders or undergoing hematopoietic stem cell transplantation (HSCT) along with more benefits in patients having respiratory system infections (80%) in comparison to bloodstream infection group (58.3%) and skin or mucous infection group (20%).

In accordance with other studies, our study showed that 28/36 (78%) patients responded to granulocyte transfusions, recovered from life-threatening infections; however, 15/28 (54%) patients died on account of the progression of their disease. Also, 8/36 (22%) of our patients showed a transient response but eventually died; only one death was due to a post GT pulmonary event.

Lee et al reported benefits of GT in gram-negative bacterial and resistant infections as compared with infections with gram-positive organisms. The difference in response is possibly due to an early uptake with persistent retention of neutrophils at gram-negative infection sites, whereas there is no increase in neutrophil uptake at gram positive infection sites.[16]

The common etiology for sepsis was gram-negative organisms at our institute.

The effectiveness of granulocyte transfusions is determined by their starting time. Early transfusion during sepsis increases the chances of survival by preventing the onset of multiorgan damage. Sachs et al showed a 92.6% overall response to early GT and a better toxicity profile. Uppuluri et al[2] reported early administration of granulocyte within 48 hours of a septic episode resulting in significant improvement in the overall survival (41% to 54%).

Garg et al[22] reported that GT within 7 days of neutropenic sepsis leads to significantly higher overall survival in patients ($p = 0.01$).

The modest survival in our study is probably due to a delay in starting GT, difficulty in finding donors, and lesser affordability.

Tandem granulocyte transfusions in neutropenic patients are effective. Seidel et al[23] reported repeated transfusion of granulocytes for 5 days with a minimum of 3×10^8/kg neutrophils/concentrate, stabilized ANC, reduced the neutropenic duration, and increased infection control.

In our study, all 8 patients who had received a single transfusion of granulocytes died.

Price et al[14] and Adkins et al[26] reported GT was well tolerated and the incidence of serious adverse events in recipients was uncommon. Chills and rigor were frequent side effects in recipients of granulocytes.

Other reported adverse events of GT are transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-associated dyspnea, hypotension, post-transfusion purpura, transfusion-transmitted infection, and risk of alloimmunization. At our center, all granulocyte collections were irradiated before transfusion to decrease the chance of alloimmunization.

Conclusion

A granulocyte therapy was effective in many critically sick patients with prolonged and profound neutropenia. Granulocyte transfusions may be more beneficial in selected patients where it provides more time to overcome refractory infections to broad-spectrum antibiotics. Granulocyte transfusion are at best a "bridge" that gives time to marrow recovery. The challenges to using GT are clinical, finding patients who may get benefitted, and logistical; selection of donors and harvest technique. Randomized trials with large numbers of patients are required to prepare guidelines for granulocyte use.

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Conflict of Interest
None declared.

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