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Survival among children and adults treated with granulocyte transfusions: Twenty years' experience at a Brazilian blood center

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ABSTRACT

Background: It remains controversial whether granulocyte transfusions as a supportive treatment improve survival in patients with febrile neutropenia or granulocyte dysfunctions. We describe survival rates subsequent to granulocyte transfusions in pediatric and adults patients treated at a major blood center in Brazil.
Material and methods: We retrospectively reviewed the clinical charts of pediatric and adult patients treated with granulocyte transfusions at our institution from January 2000 to October 2019. We assessed demographic characteristics, clinical features, indications for transfusion, units transfused, dose of granulocytes administered and survival rates 30 and 100 days after the initial transfusion.
Results: We identified 64 pediatric and 67 adult patients treated with 262 granulocyte transfusions. An optimal dose ($> 0.6 \times 10^9$ granulocytes per kilogram per transfused unit) was available for transfusion in 80.4 % of pediatric patients but in only 19.6 % of adults ($p = 0.017$). Thirty days after their first granulocyte transfusion, 38 (59.4 %) pediatric and 61 (91 %) adult patients had died. Patients receiving the optimal dose of granulocytes had better survival outcomes, but even among this sub-group, adults were more likely to die than were children either at 30 days (OR = 8.67, 95 %CI 2.69–34.9) or 100 days (OR = 6.27, 95 %CI 1.86–25.9) after their initial granulocyte transfusion.
Conclusion: Survival rates following granulocyte transfusion varied by the dose transfused and were higher in children than in adults.

1. Introduction

Prolonged neutropenia is common among patients who receive intensive chemotherapy to treat hematologic and solid tumor malignancies, as well as in those undergoing stem cell transplants. Despite the modern arsenal of antimicrobials and supportive therapy available to neutropenic patients, acquisition of bacterial and fungal infections remains associated with high morbidity and mortality [1,2]. Among neutropenic patients with severe aplastic anemia or defective granulocyte functions, infections are the most frequent cause of death [3]. Therapeutic granulocyte transfusion may increase the number of active circulating neutrophils [4] and is a logical supportive treatment approach for patients with prolonged neutropenia or neutrophil dysfunction who have, or are at risk for, infection [2,5]. However, treatment with granulocyte transfusions has not been shown to reduce overall mortality in most controlled trials [6].

Treatment of blood donors with granulocyte colony stimulating factor (G-CSF) and dexamethasone to increase granulocyte yield has

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been available for almost 30 years [7–9]. Improvements in automated blood cell separation for leukapheresis, standardization of collection protocols and enhanced training of blood center teams have resulted in more precise granulocyte collections and obtaining the optimal dose needed for each recipient. A large multicenter randomized trial that evaluated patients with febrile neutropenia who were treated with daily granulocyte transfusions plus antimicrobial treatment compared with patients receiving only antimicrobial therapy failed to demonstrate a benefit of granulocyte transfusions, but the power of the study was reduced. However, a post-hoc analysis of this study suggested that patients receiving higher doses ($\geq 0.6 \times 10^9$ granulocytes/kg/transfused unit) tended to have better outcomes than those receiving lower doses [10].

Granulocyte transfusions are time-consuming for donors, costly, dependent upon availability of qualified donors, and are not free of potential adverse effects to both donors and recipients [11,12]. Given these limitations, there is still a controversy about whether granulocyte transfusions can significantly increase the survival of patients with febrile neutropenia or granulocyte dysfunctions [13]. In this communication, utilizing data collected over a twenty-year period, we retrospectively analyzed the 30- and 100-day mortality rates after an initial granulocyte transfusion in pediatric and adult patients, and correlated outcomes with granulocyte dosage administered and with clinical characteristics.

2. Methods

We reviewed the clinical charts of 140 patients who received granulocyte transfusions at Hospital das Clínicas da Faculdade de Medina da Universidade de São Paulo, the largest public hospital in Brazil, located in São Paulo city, from January 2000 to October 2019. Nine patients (6.4 %) were subsequently excluded due to incomplete data. The study was approved by the Ethics Committee of Fundação Pró-Sangue.

We evaluated demographic characteristics, clinical features, indications for granulocyte transfusion, number of granulocytes transfused, adequacy of the administered dose and mortality rates within 30 and 100 days after the first granulocyte transfusion in adult and pediatric patients. After the first granulocyte transfusion, most patients subsequently received additional granulocyte transfusions during the study period. Pediatric patients were defined as those treated in the Pediatric Unit and < 18 years of age. Adult patients were treated in the general ward and were ≥ 18 years old. The need for therapeutic granulocyte transfusions were clinically determined by patients' physicians according to the institutional protocols for transfusion of granulocyte concentrates. For patients with severe neutropenia the criteria included all of the following : (1) Severe neutropenia, defined as an ANC $< 0.5 \times 10^9$/L [WHO 1999] due to congenital or acquired bone marrow failure syndromes; (2) receiving active treatment in an attempt to achieve disease remission; (3) proven or highly probable fungal or bacterial infection that was unresponsive to appropriate antimicrobial therapy for more than 48 h; (4) expected neutrophil recovery (ANC $> 0.5 \times 10^9$/l) in the near future and/or in whom potential curative therapy was anticipated.

Granulocyte donors were recruited primarily from voluntary platelet apheresis donors and, in a small number of cases, from relatives of the patients. Donors had to fulfil the same qualification criteria as whole blood donors, have adequate bilateral antecubital venous access for apheresis collection and be negative in all routine blood donation screening tests within 72 h before leukapheresis. Donors were stimulated with dexamethasone (8 mg PO) and/or recombinant G-CSF 300 μcg in a single subcutaneous application 12–15 h before collection, except if they had an absolute contraindication to any of these medications. The collection of granulocyte concentrates was performed with a continuous-flow cell separator (COBE Spectra Apheresis System, Terumo BCT, Tokyo, Japan or, Com.Tech-5, Fresenius Kabi, Germany or, Spectra Optia Apheresis System, Terumo BCT, Tokyo, Japan) with an average blood flow volume between 40 and 60 mL.

The following data were evaluated for each participant: gender, age, age group (pediatric vs. adult), underlying disease, indication for granulocyte transfusion, number of transfusions, frequency of transfusion-related adverse events, infection at enrollment, site of infection, and mortality rates within 30 and 100 days of hospitalization after the first granulocyte transfusion. An optimal dose was defined as $> 0.6 \times 10^9$ granulocytes per kilogram per transfused unit (8).

2.1. Statistical analysis

Summary statistics, namely frequencies, mean [standard deviation, SD] or median [range] were reported. The 30-day and the 100-day mortality rates after the first granulocyte transfusion were estimated with a 95 % confidence interval (95 % CI). Univariable prognostic analyses were conducted including all studied variables. The prognostic value was quantified by odds ratios (OR) estimated from logistic models. Multivariable logistic regression was used to define the risk of death according to age groups, adjusted for potential confounders. To ensure the absence of collinearity in the final model, the Variance Inflation Factor (VIF < 5) was checked. Odds Ratio (OR) and (95 % CI) were reported. The chi-square test was applied to assess the adequacy of dose according to age group. All statistical tests were two-sided with p-values < 0.05 denoting statistical significance. All analyzes were performed with Rstudio 1.3.959 statistical software (https://www.rstudio.com).

3. Results

Table 1 details clinical data from 64 pediatric and 67 adult patients who received 262 granulocyte transfusions. Of the pediatric patients 35 (54.7 %) were male, mean age (±SD) was 8.5 (±5.4) years old, 16 (25 %) had acute lymphocytic leukemia, 61 (95.3 %) received the transfusion to treat febrile neutropenia and 17 (26.6 %) had undergone bone marrow or peripheral stem cell transplantation. The median number of granulocyte transfusions were three (range 1−19). Among the adults, 29 (45.3 %) were male, mean age (SD) was 36.2 (13.2) years old, 28 (41.8 %) had acute myelogenous leukemia, all received their granulocyte transfusions to treat febrile neutropenia and 14 (20.9 %) had undergone bone marrow or peripheral stem cell transplantation. The median number of granulocyte transfusions was 3.5 (range 1−11). A fungal infection was identified in 20 pediatric patients (31.2 %) (Fig. 1a) and

Table 1
Characteristics of pediatric and adult patients receiving granulocyte transfusions.

	Total (n = 131)	Pediatric (n = 64)	Adults (n = 67)
Male, n (%)	71 (54.2)	35 (54.7)	29 (45.3)
Age, mean (SD)	22.6 (17.2)	8.5 (5.4)	36.2 (13.2)
Underlying disease, n (%)			
acute myelogenous leukemia	35 (26.7)	7 (10.9)	28 (41.8)
acute lymphocytic leukemia	29 (22.1)	16 (25.0)	13 (19.4)
aplastic anemia	23 (17.6)	15 (23.4)	8 (11.9)
other leukemias	9 (6.9)	5 (7.8)	4 (6.0)
solid tumor	8 (6.1)	8 (12.5)	0 (—)
Lymphoma	7 (5.3)	1 (1.6)	6 (9.0)
Other	20 (15.3)	12 (18.8)[a]	8 (11.9)[b]
Transfusion indication, n (%)			
neutropenic febrile	128 (97.7)	61 (95.3)	67 (100)
neutrophil dysfunction & infection	3 (2.3)	3 (4.7)	0 (—)
Neutropenic febrile & BMT/PBSC[c], n (%)	31 (23.7)	17 (26.6)	14 (20.9)
Number of transfusions, median (range)	3 (1−19)	3 (1−19)	3.5 (1−11)

[a] Solid tumors (n = 8) and Chronic granulomatous disease (n = 4).
[b] Myelodisplasic syndrome (n = 4) and myeloproliferative disease (4).
[c] Bone marrow transplantation/peripheral blood stem cell transplantation.

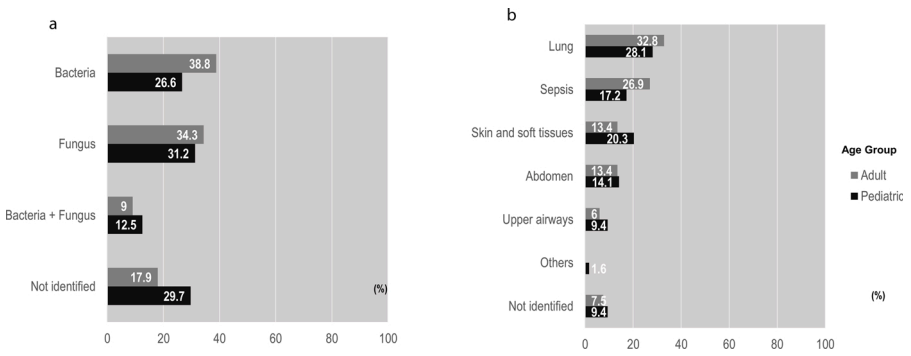

Fig. 1. (a) Infectious agents diagnosed at enrollment in pediatric and adult patients treated with granulocyte transfusions. (b) Sites of infection in pediatric and adult patients treated with granulocytes transfusions.

lung was the most frequent site of infection (28.1 %) (Fig. 1b). Twenty-six adults (38.8 %) had a fungal infection (Fig. 1a) and lung was the most frequent site of infection (32.8 %) (Fig. 1b).

Due to the smaller size of pediatric patients, an optimal dose of granulocytes ($> 0.6 \times 10^9$ granulocytes per kilogram per transfused unit) was transfused in 80.4 % of pediatric patients and in only 19.6 % of adults ($p = 0.017$). Mild and moderate adverse events (AEs) potentially related to the granulocyte transfusions were reported for nine (13.4 %) adults and one (1.6 %) pediatric patient. Among the adults five (7.5 %) experienced shivering, two (3%) developed a skin rash, one (1.5 %) had arterial hypotension and one (1.5 %) had dyspnea. The only report of an adverse granulocyte transfusion-related event in pediatric patients was a single (1.6 %) case of a febrile non-hemolytic transfusion reaction. No serious transfusion-associated AEs were reported (e.g. TRALI).

By 30 days after the first granulocyte transfusion 38 (59.4 %) pediatric and 61 (91 %) adult patients had died. At 100 days post-initial transfusion, there were no additional deaths among the adults, but an additional seven pediatric patients died. Only three patients treated with granulocyte transfusions had ongoing neutrophilic dysfunction and they all survived 30 and 100 days after receiving their transfusions.

The overall mortality rates 30 days after the first granulocyte transfusion was 90.7 % in patients transfused from June 2001 to February 2008, 73.8 % in those transfused from March 2008 to April 2014 and 64.3 % if the transfusion was from May 2015 to August 2019 ($p = 0.015$). However, when evaluated separately the 30-day mortality rates among adults and children were not statistically significant over the study time period ($p = 0.195$ and $p = 0.546$, respectively). By univariate analyses, the odds ratio to die either by 30 days (OR = 6.96 95 % CI 2.77–20.1) or 100 days (4.29 95 %CI 1.67–12.6) after the first granulocyte transfusion was higher in adults when compared with the pediatric patients. Gender, underlying disease, number of transfusions, etiology of infection and infection site were not associated with a higher mortality in 30 days and in 100 days following granulocyte transfusions (Table 2). Multivariate analyses demonstrated that among patients receiving granulocyte transfusions, adults were more likely to die than were children after 30-days (OR = 8.67, 95 %CI 2.69–34.9) Table 3 and after 100 days (OR = 6.27, 95 %IC 1.86–25.9) following their initial transfusion.

Table 2
Univariable analysis of mortality in patients treated with granulocytes transfusions.

	n	30-day mortality n (%)	Odds Ratio (95 %CI)	P-value
Gender				
Male	71	51 (71.8)	Reference	—
Female	60	48 (80.0)	1.57 (0.70–3.63)	0.280
Underlying disease				
acute myelogenous leukemia	35	28 (80.0)	Reference	—
acute lymphocytic leukemia & other leukemias	38	27 (71.1)	0.61 (0.20–1.79)	0.378
aplastic anemia	23	18 (78.3)	0.90 (0.25–3.45)	0.873
Others	35	26 (74.3)	0.72 (0.23–2.21)	0.570
Number of transfusions (median)				
≤ 3 units	67	49 (73.1)	Reference	—
> 3 units	55	45 (81.8)	1.65 (0.70–4.08)	0.259
Neutropenic febrile & BMT/PBSC[a], n (%)				
No	98	75 (76.5)	Reference	—
Yes	31	24 (77.4)	1.05 (0.42–2.92)	0.919
Infection at enrollment				
Undetermined	31	23 (74.2)	Reference	—
Bacteria	43	32 (74.4)	1.01 (0.34–2.90)	0.983
Fungus	43	34 (79.1)	1.31 (0.43–3.94)	0.623
Bacteria + fungus	14	10 (71.4)	0.87 (0.22–3.87)	0.846
Infection site				
Other	62	47 (75.8)	Reference	—
Lung	29	22 (75.9)	1.00 (0.37–2.94)	0.995
Sepsis	40	30(75.0)	0.96 (0.38–2.46)	0.926
Age group				
Pediatric	64	38 (59.4)	Reference	—
Adult	67	61 (91.0)	6.96 (2.77–20.1)	< **0.001**

[a] Bone marrow transplantation/peripheral blood stem cell transplantation.

4. Discussion

We observed a higher 30- and 100-day mortality after the initiation of granulocyte transfusions among adults when compared to pediatric patients. There was more than an eight- fold increased risk of adults to die within 30 days and a sixfold risk to die within 100 days after starting granulocyte transfusions when compared to pediatrics patients. An optimal dose was available for administration to 80.4 % of pediatric patients and to 19.6 % of adults. There were no severe adverse events reported in either group.

A recent review reported that the overall 30-day mortality in patients receiving granulocyte transfusions was 35 % [1]. In two randomized trials, mostly among adults, mortality rates 30 days after randomization varied from 20 % to 58 % [10,14] and in New Zealand, in a 16-years period study of granulocyte transfusions, survival rate was 41 % [15]. In pediatric patients who were treated with granulocyte transfusions, mortality rates 30 days after initiating treatment were lower and varied

Table 3
Multivariable analysis of mortality in patients treated with granulocyte transfusions.

	30-day mortality Odds Ratio (IC 95 %)	P-value
Gender		
Male	Reference	—
Female	2.19 (0.80–6.45)	0.136
Underlying disease		
acute myelogenous leukemia	Reference	—
acute lymphocytic anemia & other leukemias	1.71 (0.40–7.96)	0.378
aplastic anemia	1.96 (0.36–12.0)	0.446
Other	1.46 (0.34–6.62)	0.615
Number of transfusions		
$\leq$ 3 units	Reference	—
$>$ 3 units	1.62 (0.59–4.71)	0.359
Neutropenic febrile & BMT/PBSC[a]		
No	Reference	—
Yes	1.62 (0.51–6.01)	0.434
Infection at enrollment		
Undetermined	Reference	—
Bacteria	0.57 (0.14–2.15)	0.417
Fungus	1.17 (0.27–5.00)	0.828
Bacteria + Fungus	0.88 (0.15–5.34)	0.882
Infection site		
Other	Reference	—
Lung	0.54 (0.15–2.04)	0.357
Sepsis	0.72 (0.21–2.37)	0.583
Age group		
Pediatric	Reference	—
Adult	8.67 (2.69–34.9)	0.001

[a] Bone marrow transplantation/peripheral blood stem cell transplantation.

from 9 % to 23 % [3,5,16,17]. Our survival rates were lower than previously reported for both adult and pediatric patients, and the odds of dying were higher for adults. We speculate that this was due to the likelihood that adults were more seriously ill, received lower doses of granulocytes per kg body weight and their granulocyte transfusions may have been administered relatively late in the course of disease when efficacy is likely reduced. Transfusions at earlier times are associated with better outcomes [16]. An optimal dose of transfused granulocytes was reached in more than 80 % of pediatric patients but only in less than 20 % of adults. The mortality rate of all evaluated patients slightly decreased over the study time period. The average number of transfusions was low in the population, mostly due to high patient mortality and in some cases because of their recovery from neutropenia. Improvement in collection procedures and cell separators as well as advances in the earlier recognition of the need for granulocyte transfusions may have impacted the rates of survival. Additionally, new antibiotics and new approaches to the recognition and management of fungal infections could have influenced survival. Interestingly, all patients with granulocyte dysfunction survived 100 days after initiation of granulocyte transfusions. This corroborates previous studies of the efficacy of granulocyte transfusion for the treatment of patients with infections and neutrophilic dysfunctions [18,19]. Gender, underlying disease, number of transfusions, infection at enrollment and infection site were not associated with a different mortality rate when comparing adults to children. This was probably a consequence of the great variety of clinical presentations and the number of participants in the study.

There were few adverse events in the studied population and none were severe. It has been estimated that 10–40% of patients treated with granulocyte transfusions may experience an adverse event [1]. The small number of adverse events among those receiving granulocyte transfusions may also be due to the fact that these profoundly ill patients will have a number of medical complications, thus making it difficult to identify those specifically related to the transfusions. We suggest that improvements in the collection procedure with G-CSF and dexamethasone stimulation and leukapheresis collection may have lowered the incidence of adverse events in the present study. Prior non-automatized granulocyte collection methods have been associated with severe reactions [12]. Additionally, most reports regarding adverse granulocyte transfusion reactions were published more than 20 years ago [1]

We recognize limitations in our study. The study time frame was large and different therapeutics that impact patient survival, such as bone marrow transplants, new antibiotics, modern antifungal therapy, improved methods of early detection and prevention of infections, among others, may have varied during the 20-year investigation period. However, since granulocyte transfusion is not common in routine medical practice, a comprehensive evaluation of survival is only possible over a long period of time. In addition, the dose of granulocytes transfused to the adults in our patient population was less than optimal in more than 80 % of cases. This most likely influenced the rate of mortality. The low incidence of transfusion-related adverse events in our pediatric patients may have been at least partially due to underreporting, as most of these patients had severe disease and received additional treatments that are not devoid of adverse events. This may have masked adverse events associated with the granulocyte transfusions [10,17]. Our study was retrospective and may have been unintentionally biased in the absence of pertinent data. This limitation is intrinsic in retrospective observational studies. We included all variables present in patients' charts to minimize misinterpretation during data analysis. The recruitment of appropriate donors and stimulation of granulocytes production and their collection are time-consuming and impact the lag period between indication for transfusion and the transfusion itself. We acknowledge and highlight this limitation and wish to emphasize the need to improve the overall protocol to shorten the time between collection of more adequate doses of granulocytes and their delivery to patients. Finally, data on granulocyte recovery after transfusions was not systematically collected and, as our study is retrospective, we were unable to quantitatively evaluate the efficacy of transfusion in elevating neutrophil levels in our subjects.

We conclude that there was an overall low survival rate among patients receiving granulocyte transfusions at our center. However, survival was highest in the pediatric population and among individuals receiving elevated doses of granulocytes. This supports the likely benefit of higher transfusion granulocytes doses in improving survival among infected patients with neutropenia and neutrophilic disfunction. Although these findings support the continued utility of this intervention for selected patients, randomized trials are still required to ultimately determine if granulocyte transfusions improve survival among infected neutropenic and neutrophil dysfunctional patients.

CRediT authorship contribution statement

Cesar de Almeida-Neto: Conceptualization, Data collection, Designed the research project, Methodology, Writing and review the manuscript. **Lucas Machado Corso**: Designed the research project, Data collection and Data management; **Lucas Bassolli de Oliveira Alves**: Statistical analyses and review of the manuscript; **Steven S. Witkin**: Manuscript writing, draft preparation, Supervision and review of the maniscript; **Debora Toshie Hamasaki:** Data collection, performed the research; **André Luís Albiero**: Data collection, draft review and manuscript writing ; **Caroline Limoeiro Manangão**: Data collection, draft review and manuscript writing, **Alfredo Mendrone-Junior**: Data review, data validation and review of the draft, **Vanderson Rocha**: Supervison, Reviewing the original manuscripit and designed the research.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

All authors fulfil the following three criteria: Substantial

contributions to research design, or the acquisition, analysis or interpretation of data, drafting the manuscript or revising it critically, and approval of the final submitted version. CAN, ALA, LMC, DTH, CLM performed the research; CAN, LMC, LB, VR, AMJ designed the research study; VR, AMJ, CAN, LMC, LB, DTH analyzed the data, CAN, SSW, LB wrote the paper.

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