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Granulocyte transfusions in patients with chronic granulomatous disease and refractory infections: the NIH experience

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Summary

Granulocyte transfusions are a relatively safe adjunctive therapeutic option for patients with chronic granulomatous disease and severe/refractory bacterial or fungal infections. Early initiation, high frequency and sustained therapy is associated with significantly better outcomes.

Keywords

NADPH oxidase; superoxide; DHR; granulocyte transfusion; chronic granulomatous disease

To the Editor

Although its efficacy has not been definitively proven, granulocytes transfusions (GT) are used as an adjunctive therapy to antimicrobials in the treatment of patients with severe or treatment refractory infections in the setting of neutropenia or granulocyte dysfunction, as in chronic granulomatous disease (CGD).[1–4] Despite new and improved antimicrobial prophylactic and therapeutic measures, severe infections continue to be life-threatening and the main cause of death in CGD patients.[5]

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We retrospectively reviewed the medical records of CGD patients with severe and refractory infections who received GT at the National Institutes of Health (NIH) Clinical Center, from 1984 to 2012. All patients had CGD confirmed by molecular, immunoblot and/or NADPH-oxidase functional assays; all were consented to NIH research protocols. Patient demographics were analyzed based on gender, CGD genotype, and age at GT use. Infections were classified based on: a) affected site; b) extent (localized vs. disseminated), and; c) microbiology.

GT data was analyzed based on the total number of transfusions per cycle, the periodicity of transfusions, and the median number of granulocytes/kg/transfusion. Each GT cycle was considered an independent course aiming to treat a particular infection. Adverse events (AE) associated with GT were also analyzed. All patients were treated with antimicrobials before, during and after the GT based on organism speciation and sensitivity. Debulking surgery to remove infected tissue was performed before, during and after GT as clinically indicated. GT was utilized in patients when medical and/or surgical treatments failed to control underlying infections.

GT treatment initiation was categorized as early (≤1 month) or delayed (>1 month) after infectious disease clinical/microbiologic diagnosis. Infection outcome/efficacy following GT was categorized as cleared (CL), partially cleared (pCL) or not cleared (nCL). An infection was considered CL after GT when complete clinical and microbiologic resolution were achieved. A pCL infection was defined as overall clinical and/or microbiologic improvement in the patient's status. A nCL infection was defined as clinical and/or microbiologic progression following GT, or if the patient died from the infection. Categorical variables were presented as totals and percentages. Continuous variables were summarized by median and range. Statistical analysis of all continuous variables was carried out using the Mann–Whitney test, and all categorical variables that potentially impacted outcome were analyzed using Chi-square or Fisher's exact tests depending on sample size. All reported p values are two-sided using a level of significance of 0.05. Data analyses were generated using PRISM 6 for MAC OSX.

Sixty-nine GT courses aiming to treat equal number of refractory infections were utilized in 48 CGD patients over a 29-year period at the NIH (NIH CGD cohort, n=234). GT in the context of hematopoietic stem cell transplantation (HSCT; n=7) were excluded from all analysis; GT associated with early onset AE precluding further transfusions (n=4, 6.5% of 62 GT courses initiated; range, 2–6 total transfusions in 2–11 days) were excluded from efficacy analysis. Finally, 58 GT courses in 40 CGD patients [22 X-linked (*CYBB*/gp91^{phox}), 17 autosomal recessive (14, *NCF1*/p47; 2, *CYBA*/p22^{phox}; and 1, *NCF3*/p67^{phox}) and one extremely lyonized X-linked CGD female carrier] were analyzed. Eight CGD patients received multiple GT courses (range, 2 to 6) to treat different infections. Nine females and 31 males were treated. Microbiology was definitive in 51/58 infections reviewed (88%), the majority fungal. Debulking surgery (resection or debridement) was performed in 16 cases (30%), either during or immediately after the GT course. GT were associated with CL (n=42) or pCL infections (n=9) in 51/58 (88%) episodes. Of the 7 nCL infections, 6 (1 bacterial, 4 fungal, and 1 polymicrobial) caused the patient's demise. Two of these patients had prior infections CL after GT. GT therapy was more frequently used before

2002 (51 courses, average 2.8/year) than thereafter (7 courses, average 0.7/year). GT showed an overall efficacy of 94% for CL+pCL infections before 2002, which decreased to 43% since 2002.

To examine efficacy, the 58 GT-treated infectious episodes were stratified into those that improved after GT therapy (CL+pCL) vs. those who did not (nCL) (Table 1). The overall success rate associated with GT in microbiologically confirmed infections was not significantly different between fungal (82%) and bacterial (94%) infections. The efficacy of adjunctive GT therapy was independent of CGD genotype: 87% of infections CL+pCL in X-linked CGD patients, as did 88% of infections in patients with autosomal recessive disease (p=1). When we compared patients who CL+pCL vs. nCL their infections, the first group received significantly more (≥ 25 vs. 15 transfusions) and more frequent transfusions (≤ every 2 days vs. > every 2 days). Despite changes in methods for granulocyte collection (dexamethasone alone until 1995, dexamethasone and granulocyte-colony stimulating factor thereafter), all patients received high dose GT (median, $\geq 0.6 \times 10^9$ granulocytes/kg/transfusion) and no significant differences were detected between groups. Patients who had CL+pCL were younger than those who had nCL infections (median, 14 vs. 30 years). Patients starting early GT therapy were significantly more likely to have CL+pCL infections than those in whom GT initiation was delayed (≤1 month vs. >1 month).

A total of 1594 individual GT were used on the 58 GT courses analyzed. AE were reported in 31 of the 1594 individual transfusions (1%), affecting 12 patients (29%), none of them lethal. All recorded AE included fever and/or chills either alone or associated with rigors, flushing, vomiting, irritability, or agitation. Two patients developed transient dyspnea, one of whom was reported as TRALI (Transfusion-related acute lung injury). Thirteen patients developed anti-HLA antibodies, six of whom also showed anti-RBC antibodies. Three other patients developed only anti-RBC antibodies. As mentioned above, GT were stopped after 4 AE, 2 of them occurring in the same patient while treating different infections.

Our single center retrospective study of GT as an adjunctive therapy in CGD patients with refractory infections showed that overall >80% infections improved with this approach. GT were more often associated with favorable outcomes when transfusions were implemented early in the course of illness and when the number of infusions was higher. These results were independent of the CGD genotype, whether fungi or bacteria caused the infection, the site of infection, or whether it was localized of disseminated.

Since 2002 the overall use of GT declined in our center. Multiple variables have likely influenced this change in practice, including increased use of HSCT as a curative approach. HSCT has also been used to successfully treat severe infections in CGD not responding to conventional therapy.[6] In addition, with the increased use of HSCT, there has been avoidance of GT due to the attendant risk of HLA allo-sensitization, a major complication for HSCT.[7] Finally, the availability of more effective anti-bacterials and anti-fungals[8] may have led to fewer severe/refractory infections requiring GT. Therefore, with the confounding changes in practice and treatment, it is difficult to compare the intervals of GT use.

Whether the use of GT is causally associated with better outcomes or simply a marker for better survival, cannot be determined based on the retrospective nature of this study and the intrinsic limitations of the analysis performed. It is formally possible that those patients who better tolerated GT and who were able to receive more infusions were less sick at the outset and who had slow but successful responses to other antimicrobial therapies. The association of better outcomes with younger age may correlate with less underlying end-organ damage, and reflect the overall low mortality in childhood. [9] However, our data suggest that GT is relatively safe with few significant complications.

This is the largest cohort of CGD patients treated with GT. Based on previous selected cases, there was insufficient evidence to support routine use of GT in the treatment of refractory infections in CGD. Our single center experience suggests, although does not formally prove, that timely, frequent and sustained GT is relatively safe and associated with better outcomes. Allo-immunization remains a concern for those patients anticipating HSCT[7].

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Table 1

Granulocytes transfusions in CGD patients, characteristics

GT Characteristics n=58		**Improved n=51**		**Not Improved n=7**	**Efficacy/significance**
		Cleared Infection (CL) n=42	**Partially Cleared Infection (pCL) n=9**	**Not cleared Infection (nCL) n=7#**	**[CL+pCL] vs. [nCL]**
Age at GT [in years]*	16 (2–63)	14 (2–38)	16 (5–30)	30 (12–63)	**0.003**
Number of GT*	27 (2–150)	29 (2–150)	25 (6–63)	15 (4–27)	**0.01**
Administration period [in days]*	48 (2–287)	50 (2–287)	50 (9–168)	37 (7–72)	0.3
Frequency [in days]*	1.8 (1–8.5)	1.7 (1–8.5)	1.8 (1.1–4.6)	2.2 (1.2–3)	**0.01**
Median number of granulocytes/kg	0.9×10^9	0.8×10^9	1.0×10^9	0.9×10^9	0.59
Early/Delayed GT initiation	32/26	26/16	5/4	1/6	**0.03**
Type of Infection					
Localized	40 (69%)	30	7	3	
Disseminated	18 (31%)	12	2	4	0.18
Lung	37 (64%)	29	4	4	
Liver	15 (26%)	9	4	2	
SNC	2 (3%)	2	0	0	
Bones	2 (3%)	2	0	0	
Lymph Nodes	2 (3%)	1	0	1	0.63
Fungal	28 (48%)	19	4	5	
Bacterial	19 (33%)	15	3	1	
Polymicrobial	4 (7%)	2	1	1	
No isolate	7 (12%)	6	1	0	0.37

GT, granulocyte transfusions

*Mean (range)

#Out of the 7 patients who did not cleared their infection after GT, 6 died. The cause of death was bacterial in 1 (*Burkholderia pseudomallei*), fungal in 4 (*Paecilomyces variotii* in 1, *Aspergillus tanneri* in 1, *Phaeoacremonium parasiticum* in 1, *Aspergillus fumigatus* in 1), and polymicrobial in 1 (*Staphylococcus aureus* + *Aspergillus flavus* + *Rhizopus microsporus* + *Paecilomyces variotii*); the 7th patient (infected with *Mucor* spp.) improved after further antifungal and surgical treatment. None of these patients experienced AE to GT.