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ORIGINAL ARTICLE

Clinical experience of granulocyte transfusion in the management of neutropenic patients with haematological malignancies and severe infection

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Abstract

Background: Prolonged chemotherapy-induced neutropenia is a major risk factor for the development of severe bacterial and fungal infections. Infectious manifestations may progress despite adequate anti-infectious treatment and lead to a very high short-term mortality. Granulocyte transfusion (GT) therapy is often considered. However, its efficacy is not well documented. *Methods:* We retrospectively analyzed the clinical characteristics and outcome of a cohort of patients with haematological malignancies receiving GT during neutropenia and severe infection. *Results:* A total of 30 patients with a median age of 46 y (range 3–82 y) who had received 1 or more GT were included. Acute leukaemia (80%) and non-Hodgkin lymphoma (17%) predominated as the underlying malignancy. All patients had severe and prolonged (median 16 days) neutropenia. The major indications for GT were persistent fever and clinical deterioration despite broad anti-infectious therapy, in combination with progressive pneumonia ($n = 16$), neutropenic enterocolitis ($n = 6$), and soft tissue infections ($n = 3$). GTs were given for a median of 3 transfusions (range 1–14). The median time to fever defervescence after GT was 14 days (range 6–33 days). For 11 patients, the resolution of fever and all signs of infection could directly be related to GT, and 3 of these patients became long-term survivors. Mortality at 30 days post-GT was 40% and at 6 months post-GT was 72%. GT was well tolerated. *Conclusions:* A substantial proportion of severely ill neutropenic patients appeared to benefit from GT. The results further underline the need for well-designed, randomized, prospective trials to determine the efficacy of this intervention in patients with life-threatening infectious complications.

Keywords: *Febrile neutropenia, granulocyte transfusion, haematological malignancies*

Introduction

Infection associated with chemotherapy-induced neutropenia continues to be a major cause of morbidity and mortality in patients treated for haematological malignancies [1,2].

During recent years, the use of more intensive chemotherapy also at older age has rendered patients neutropenic for longer periods of time. Prolonged and profound neutropenia remains the major risk factor for the development of severe bacterial and fungal infections [1,3]. A parallel improvement in general supportive care and intensive care together with the empirical use of broad-spectrum antibiotics and the introduction of new effective antifungal agents have contributed to a significantly increased survival in this clinical setting. However, in some severely neutropenic patients, infectious manifestations progress despite adequate anti-infectious treatment. These patients have a very high short-term infection-related mortality [4]. Granulocyte transfusion (GT) therapy may thus be a clinically feasible and logical approach to support these patients.

The concept of GT therapy was introduced in the 1960s [5]. Granulocytes harvested from healthy community donors have been used in patients with chemotherapy-induced neutropenia in various

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studies as a primary or secondary prophylaxis, but more commonly as a treatment modality in combination with anti-infectious therapy [6–9]. However, data regarding the potential clinical efficacy of GT therapy have been derived only from case reports and smaller controlled or uncontrolled series [10,11]. Furthermore, the majority of these studies were conducted before the era of growth factors and new antifungal agents.

Until the most optimal use of GT therapy is defined through larger randomized controlled trials, we believe that there is value in reporting a single-centre experience with this treatment modality. Thus, we retrospectively analyzed the clinical characteristics and outcome of a well-defined cohort of patients with haematological malignancies receiving GT treatment during profound neutropenia and severe infection.

Patients and methods

Patients treated for haematological malignancies at the Department of Haematology, Karolinska University Hospital during a 12-y period (1994–2006), who received at least 1 GT, were included in this retrospective study. The charts of these patients were reviewed and detailed clinical and laboratory characteristics were recorded. Major reasons for GT therapy were identified. Details regarding the GT processing for each patient were obtained from the database of The Department of Immunology and Transfusion Medicine. Positive microbiological cultures obtained within 1 week before and during the admission were noted irrespective of whether they were related to the major indication for the given GT or not.

The major outcomes studied were tolerability to GT, clinical response (defined on a clinical basis as the resolution of fever and all clinical signs of infection in direct association with the GT therapy), and short-term (30-day) survival. Data were expressed as the mean ($\pm$ standard deviation, SD) or as the median (range). The Chi-square test or Fisher's exact test, when appropriate, was used to compare proportions, and the Student's *t*-test was used for the comparison of means. A *p*-value of <0.05 was considered significant. The regional ethics committee approved the study.

Results

A total of 30 patients with a median age of 46 y (range 3–82 y) who had received 1 or more GT were included. Acute leukaemia (80%) and non-Hodgkin lymphoma (17%) predominated as the underlying haematological malignancy. All patients had severe (absolute neutrophil count (ANC) $<0.1\times10^9$/l) and prolonged (median 16 days, range 6–63 days with ANC $<0.5\times10^9$/l) neutropenia. In 28 patients (93%) neutropenia was induced by chemotherapy, including 6 patients who underwent allogeneic stem cell transplantation. Detailed patient characteristics are given in Table I. Microbiologically verified infections were reported in 20 patients (66%) and 19 of these had bacteraemia. A total of 11 patients had invasive fungal infections and 7 patients had clinically significant viral infections (Table II). The major indications for GT therapy were persistent fever and clinical deterioration despite broad

Table I. Clinical characteristics of 30 neutropenic patients receiving granulocyte transfusion therapy.

Characteristic	
Age, y, median (range)	46 (3–82)
Male/female, *n*	15/15
Underlying disease, *n*	
Acute myelogenous leukaemia	17
Non-Hodgkin lymphoma	5
Acute lymphoblastic leukaemia	7
Amegakaryocytic thrombocytopenia	1
Positive bacterial isolate, *n*	20
Bacteraemia	19
Invasive fungal infections, *n*	
Possible	7
Proven/probable	4
Microbiologically/clinically documented viral infection, *n*	7
Cytomegalovirus	4
Adenovirus	1
Herpes simplex	1
HHV-6	1
Chemotherapy within 4 weeks prior to admission, *n*	28
Given cytostatic regimen, *n*	
Induction/reinduction regimen for acute leukaemia	15
Consolidation regimen for acute leukaemia	3
Allogeneic haematopoietic stem cell transplantation	6
Autologous haematopoietic stem cell transplantation	1
Second/third-line treatment for lymphoma	4
None	1
Number of changes/modification done in antibacterial therapy prior to GT, median (range)	3 (1–7)
Severe neutropenia (ANC $<0.1\times10^9$/l), *n*	30
Duration of neutropenia, days, median (range)	16 (6–53)
Systemic treatment with antifungal agent, *n*	21
Growth factor treatment (G-CSF), *n*	27
Total duration of fever, days, median (range)	16 (5–43)
Duration of fever before GT, days, median (range)	9 (2–17)
Time to fever defervescence after GT,[a] days, median (range)	14 (6–33)

ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; GT, granulocyte transfusion; HHV, human herpesvirus.
[a]Surviving patients.

Table II. Isolated microorganisms (blood cultures) in 19 patients with microbiologically verified infections.

Microorganism	Number of positive isolates
Escherichia coli	6
Enterococcus spp.	3
Coagulase-negative staphylococci	3
Alpha-haemolytic streptococci	3
Pseudomonas aeruginosa	3
Staphylococcus aureus	2
Klebsiella spp.	2
Other	2
Stenotrophomonas maltophilia	1
Streptococcus pneumoniae	1
Total	26

antibiotic therapy, in combination with progressive pneumonia ($n = 16$), neutropenic enterocolitis ($n = 6$), or soft tissue infections ($n = 3$) (Table III). All patients received ongoing combination antibiotic treatment prior to and during GT treatment and 21 (70%) patients were on systemic antifungal therapy.

Granulocyte donation

Granulocytes were collected from ABO- and Rhesus D-compatible healthy blood donors. Stimulation of granulopoiesis was done by granulocyte colony-stimulating factor (G-CSF, standard dosage of 300 μg given as a single subcutaneous injection the evening before donation) and corticosteroids (hydrocortisone 100 mg as a single intravenous injection 15 min before donation). Granulocytes were collected by apheresis technique on the day of transfusion, irradiated with 25 Gy after apheresis, and were transfused into patients through a standard transfusion set. No premedications were given routinely.

Granulocyte transfusion therapy

GTs were given daily or every other day for a median of 3 transfusions (range 1–14). The average neutrophil content per transfusion was $35 \times 10^9 \pm 13 \times 10^9$ (SD). A detectable increment in neutrophil count the day after GT occurred in 62% of patients and the median time to defervescence of fever after GT in patients surviving the febrile neutropenia episode was 14 days (range 6–33 days). For 11 (37%) patients the resolution of fever and all signs of infection seemed be directly related to GT treatment and 3 (10% of all patients) of these patients became long-term survivors (> 5 y). Mortality at 30 days post-GT was 40% and at 6 months post-GT was 72%. In non-responding patients the final cause of death was documented as infection or combined infection and progressive disease in 13/19 cases (68%). All mortalities in responding patients were due to progressive haematological malignancies and no infection-related mortality was reported in this subgroup. Patients who responded clinically to GT treatment did not differ significantly from non-responding patients with regard to age (49.9 y vs 46.9 y), number of GTs given (mean 3.2 transfusions vs 3.7 transfusions), mean dosage of neutrophils per transfusion (mean 35.4×10^9 vs 36.4×10^9), or duration of fever prior to GT therapy (8.4 days vs 9.5 days) ($p > 0.05$ for all). However, responding patients had a shorter duration of neutropenia prior to GT treatment (mean 15 days $\pm$ 6 vs 28 days $\pm$ 16, $p = 0.015$). GTs were well tolerated and no severe adverse events to GT were reported. Only 2 patients needed antihistamines/corticosteroids to avoid the recurrence of moderate allergic or febrile reactions.

Table III. Primary reason/indication for granulocyte transfusion.

Reason	*N*
Pneumonia resistant to therapy	16
Neutropenic enterocolitis/acute abdomen	6
Soft tissue infections resistant to therapy	3
General deterioration/no other specific reason	2
Septic pre-shock	1
Sinusitis resistant to local and systemic therapy	1
Meningoencephalitis	1

Discussion

In a well-defined cohort of severely ill neutropenic patients with haematological malignancies having infectious complications we demonstrated a good feasibility of GT therapy and signs of clinical efficacy.

The utility of GT therapy in treating serious infectious complications in patients with neutropenia has been studied extensively. However, the huge heterogeneity in study populations, types of infection, antimicrobial therapy, and dosage of transfused granulocytes, together with the lack of randomization, power, and universal outcome parameters, make it difficult to draw conclusions and give accurate recommendations. The optimal strategy for the use of GT therapy remains to be determined [12]. The only reported powered randomized phase III study of therapeutic GT was closed prematurely due to a very low recruitment rate resulting in inconclusive data [13]. In one of the Cochrane reviews by Stanworth et al. the authors included 8 controlled trials with 310 patient episodes. They concluded that "Currently, there is inconclusive evidence from randomized controlled trials to support or refute the generalized use of GT therapy", and that "well designed prospective studies are required" [10,14].

In this study a substantial proportion (37%) of included patients with severe infectious complications showed a clinical response. This is in accordance with results from other studies [6,15]. Three of 11 responders became long-term survivors, clearly indicating that GT therapy might be life-saving. Both short-term and long-term mortalities were extremely high in this patient population. This cannot be interpreted as indicative of the inefficiency of GT therapy. Patients with severe prolonged neutropenia, uncontrolled infectious complications, and uncontrolled underlying malignancies usually have a dismal prognosis. Moreover, all mortalities in responding patients were related to progressive malignancy and not to infection.

GTs were well tolerated and no serious transfusion reactions such as pulmonary manifestations were observed. This is in accordance with previous observations where serious toxicity was rarely encountered in recipients [15,16]. At our centre, all patients with haematological diseases are routinely given leukocyte-depleted blood products. This may contribute to a reduced risk of allo-immunizations and transfusion reactions.

We are aware of the limitations of this study – the retrospective approach, limited number of included patients, and the expected variation in decision-making regarding the initiation of GT. However, with the present shortage of data from well-designed controlled studies we believe results from cohort studies and related conclusions are worth sharing.

GTs are also used in other settings. Kerr et al. gave GT prophylactically to patients at highest risk of invasive fungal infections and compared their study group with a control group [17]. They demonstrated a modest reduction in incidence and duration of febrile neutropenia in patients receiving GT prophylaxis. Oza et al. reported similar results when GT was given prophylactically after allogeneic peripheral stem cell transplantation [7]. The cost-effectiveness of these prophylactic GT strategies has been questioned [18]. GT therapy has been used for the treatment of patients with invasive fungal infections with contradicting results [19,20]. Moreover, these trials were conducted prior to the availability of new antifungal agents such as the echinocandins and the third-generation triazoles. Another setting has been the use of GT as an additional empirical therapy for febrile neutropenia where GT is added to empirical broad-spectrum antibiotics. In the case-controlled study by Hübel et al. the fraction of patients with progressive infections turned out to be greater for patients receiving GT and no improvement in the overall survival rate was reported [21]. Accordingly, the contradicting results from these studies together with the positive findings in our study and many other studies support the notion that GT therapy is, most probably, most beneficial in the setting of patients with prolonged febrile neutropenia suffering from severe complicated infections [22].

Previous studies have demonstrated that the dose of transfused granulocytes is of importance for the clinical response [23,24]. This was confirmed by the Cochrane review done by Stanworth et al. [10]. Doses below $10 \times 10^9/m^2$ of body surface area have not been associated with improvement of established infections in the recipients. In our study we did not observe such an impact of granulocyte dosage, as almost all patients received 'adequate doses' of neutrophils. Moreover, the size of the study population and the heterogeneity of GT regimens used in the different patients limit the possibilities for drawing accurate conclusions regarding this issue. It is well established that the severity and duration of neutropenia have a determining impact on infectious complications [1]. Hence an 'adequate' granulocyte dose should always be asked for, as this is now possible thanks to the effective mobilizing procedures using growth factors and corticosteroids.

G-CSF is today the growth factor of choice for the stimulation and mobilization of granulocytes in healthy donors. It enables the collection of great numbers of granulocytes per single apheresis session. Bone pain and a flu-like illness are often reported as mild and reversible adverse events. However, very rare cases of severe adverse events such as thrombosis and splenic rupture have been reported [25]. Theoretically, there are also some concerns regarding the long-term effect of G-CSF on the donor's bone marrow, and controversy still exists over the appropriateness of this procedure. However, safety data have been reassuring to date and no causal relationship with haematological malignancies has been demonstrated [26–28]. Long-term follow-up programs are ongoing at many centres.

Patients who responded to GT therapy and recovered from their infection had a shorter duration of neutropenia. This finding confirms previous observations that the failure of bone marrow recovery is associated with significantly worse outcomes even in patients receiving GT [29,30].

In conclusion, a substantial proportion of severely ill patients with complicated febrile neutropenia benefited from GT therapy. Despite a high mortality, the presence of long-term survivors motivates further efforts to perform well-designed, randomized, prospective trials to determine the efficacy of this intervention in patients with haematological malignancies.

Declaration of interest: The authors have no commercial relationship or potential conflict of interest related to this study to declare. No funding was received for conducting this study.

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