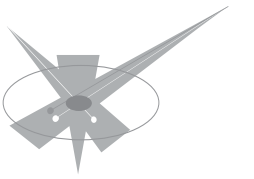
Rep Pract Oncol Radiother, 2007; 12(3): 159-162



Review Paper

Received: 2007.01.17
Accepted: 2007.05.28
Published: 2007.06.29

Granulocyte transfusion in paediatric haemato-oncology and haematopoietic stem cell transplantation

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background Severe bacterial and fungal infection remains a persistent cause of morbidity and mortality in severely neutropenic patients undergoing intensive chemotherapy and/or haematopoietic stem cell transplantation

Aim To analyze granulocyte source, collection and storage as well as clinical efficacy and toxicity of modern granulocyte transfusions for treatment of severe bacterial and fungal infections in neutropenic patients undergoing intensive chemotherapy and/or haematopoietic stem cell transplantation.

Materials/Methods A review of PubMed references based on evidence-based recommendations and own experience.

Results A single dose regimen of subcutaneous G-CSF plus oral dexamethasone administered 12 hours prior to leukapheresis appears to be a cost-effective regimen for mobilizing granulocytes from normal donors. Modern continuous flow centrifugation is used to collect granulocytes, whilst a sedimenting agent such as hydroxyethyl starch removes erythrocytes. If required storage at 10°C rather than 22°C better preserves function of collected granulocytes for up to 24 hours. Peters et al. (1999) treated 30 children for documented infection, with just over half receiving G-CSF stimulated donor granulocytes. In this series 82% of bacterial and 54% of fungal infections responded. In the Netherlands 18 children have been treated with granulocyte transfusions. In children with established infection 75% responded. Transfusion reactions associated with mobilized granulocyte transfusions are similar to other blood components, and are generally mild.

Conclusions Modern granulocyte transfusions are a relatively safe albeit controversial modality of treatment. Reasonable indications are resistant severe bacterial infection with no response to antibiotics and localized fungal infections in neutropenic patients as well as neutropenic typhilitis. The efficacy in treating or preventing sepsis remains to be established in prospective controlled trials. Within the paediatric setting, literature other than in neonates is relatively sparse and deserves further clinical studies.

Key words granulocyte transfusion • neutropenic children • bacterial and fungal infections

Full-text PDF: http:/www.rpor.pl/pdf.php?MAN=10529
Word count: 749
Tables: –
Figures: –
References: 20

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Background

Severe bacterial and fungal infection remains a persistent cause of morbidity and mortality in severely neutropenic patients undergoing intensive chemotherapy and/or haematopoietic stem cell transplantation.[1,2]

Early trials of granulocyte transfusions (GTs) demonstrated variable efficacy, mainly due to variation in the number of granulocytes infused, as well as improved antibiotic regimens for relatively good risk patients, which obfuscated any potential clinical advantage.[3,4] These and reports of adverse effects in the granulocyte transfused patients [5] led to the idea that GTs were expensive and ineffective.

Materials and Methods

References were retrieved using the online database of the National Library of Medicine (PubMed; *http://www.ncbi.nlm.nih.gov/PubMed*). Terms used included: granulocyte transfusion, neutropenic children, bacterial and fungal infections. The retrieved references were supplemented by references from the author's own database.

Results

Granulocyte source

Historically, large doses of cells were obtained from patients with chronic myeloid leukaemia and defervescence of infection was related to the number of granulocytes administered.[6] This clinical observation was also evident in the neonatal setting where the cell dose per kilogram body weight was much higher.[7]

Methodological improvements, especially G-CSF to stimulate normal donors and improvements in continuous flow separation, erythrocyte sedimentation techniques and storage, have resulted in a process whereby sufficient blood neutrophils (up to 80×10^9) can be released for potentially effective control of life-threatening infections.[8,9]

A single dose regimen of subcutaneous G-CSF plus oral dexamethasone administered 12 hours prior to leukapheresis appears to be a cost-effective regimen for mobilizing granulocytes from normal donors.[10] Although community donors could be used [11], most blood transfusion centres have used relatives as the donor source.

Granulocyte collection and storage

Modern continuous flow centrifugation is used to collect granulocytes, [12] whilst a sedimenting agent such as hydroxy-ethyl starch removes erythrocytes. Presently granulocytes are collected and administered daily with minimal time delays between collection and transfusion. Recent studies suggest that, if necessary, storage at 10°C rather than 22°C better preserves function of collected granulocytes for up to 24 hours. [13]

Discussion

Clinical efficacy of transfused granulocytes

Although it is evident that large doses of granulocytes can be collected after mobilization and that infusion results in an increased patient neutrophil count with apparently normal function, the proof that this therapy is clinically useful has not yet been established. To date evidence derives only from clinical reports or uncontrolled series. A phase III randomized trial is currently seeking approval within the USA, which aims to recruit over 200 patients over 3–4 years. [14]

In 1995, Strauss analyzed the then published results of GTs in neutropenic patients. Overall, 62% of 206 patients with bacterial sepsis apparently benefited from GTs, whereas 71% of 63 patients with invasive fungal infections reportedly did not.

In subsequent studies where higher levels of mobilized granulocytes were transfused, therapeutic

outcome of bacterial sepsis was generally favourable. Results in patients with invasive fungal infections varied depending on the study [11,15–17].

Peters and colleagues treated 30 children for documented infection, with just over half receiving G-CSF stimulated donor granulocytes. In this series 82% of bacterial and 54% of fungal infections responded.[18] In the Netherlands we have adopted a national protocol for children, which to date has treated 18 children with 21 courses of GTs. In children with established infection (n=16), 75% responded. Four children received pre-emptive GTs pre-allogeneic or autologous transplantation (two of whom had received previous GTs in the treatment group). No disseminated infection was recorded in this high-risk group.[19]

Toxicity of granulocyte transfusions

Transfusion reactions associated with mobilized GTs are similar to other blood components and are generally mild. Mobilized GTs may transmit infectious diseases; thus blood donor counselling and screening are mandatory to eliminate high-risk donors.

Recent studies have not documented pulmonary reactions with G-CSF mobilized granulocytes even in patients receiving Amphotericin B or its liposomal formulation.

Allo-immunization to HLA-class I and/or granulocyte specific antigens are a concern [20]. Rapid allo-immunization seems less common in the severely immuno-suppressed [9]. Current practice is to test for ABO antigen compatibility and leuco-agglutination prior to GTs. Acute GVHD from infusion of immune competent donor T cells can be reduced by irradiation (15–30Gy) immediately prior to administration.

Conclusions

Modern GTs are a relatively safe albeit controversial modality of treatment. Reasonable indications are resistant severe bacterial infection with no response to antibiotics and localized fungal infections in neutropenic patients as well as neutropenic typhilitis. The efficacy in treating or preventing sepsis remains to be established in prospective controlled trials. Within the paediatric setting, literature other than in neonates is relatively sparse and deserves further clinical studies.

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