Changing Trends in the Use of Granulocyte Transfusions in Neutropenic Children with Sepsis in India

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Abstract We present our data on granulocyte transfusions in children undergoing treatment for cancer and HSCT at our centre and their changing indications. In this retrospective observational analysis of children who received granulocytes from 2007 to 2015, we divided children receiving granulocytes into two groups—the first from January 2007 till December 2013 and the second from January 2014 till December 2015. This division is based on the change in our policy to use granulocytes within 48 h of septicemia as the incidence of drug resistant bacterial strains had increased at our centre. Data on 72 children with febrile neutropenia treated with 230 granulocyte infusions was analyzed. From 2007 to 2013 ($n = 48/72$), 27/48 (56 %) had culture proven sepsis of which 14 (51 %) were carbapenem resistant gram negative bacilli. 11 of the

27 children survived the crisis (41 %). We then changed our policy to transfuse granulocytes early during sepsis. From 2014 to 2015 ($n = 24/72$) 22 patients had culture proven sepsis (91 %) of which 20 had carbapenem resistant gram negative bacilli. 12/22 (54 %) with culture proven sepsis survived the episode. The survival rate improved from 41 % in first group to 54 % after early intervention with granulocytes (P value 0.0347). Despite the increased incidence of resistant bacteria during the period of 2014–2015, early use of granulocytes improved survival rate from 41 to 54 %. This intervention cannot be taken in isolation and needs to be offered early in parallel with appropriate antibiotics.

Keywords Neutropenic sepsis · Drug resistant bacterial infection · Granulocyte transfusion

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Introduction

Neutropenia follows most chemotherapy regimens used for the treatment of childhood cancers and hematopoietic stem cell transplantation (HSCT). Febrile neutropenia can range in severity from being mild with response to oral antibiotics to severe requiring prolonged antibiotics and high levels of supportive care. Advances in antibiotic and antifungal therapy help provide optimal supportive care. However, unrestricted use of antibiotics has resulted in an increase in drug resistant bacterial infections all across India. An important component of supportive care in combating these infections includes the use of granulocyte transfusions. Studies have been published demonstrating their safety and efficacy. We present our data in 72 children treated in our unit over the last 8 years with particular

reference to the changing indications for these transfusions and their efficacy in tiding over septic crisis.

Patients and Methods

We conducted a retrospective, uncontrolled, observational analysis of children undergoing treatment for hemato-oncological conditions at our centre from 2007 to 2015, who received granulocytes. We divided children into two groups, the first group being those receiving granulocytes from January 2007 till December 2013 and the second group being those receiving granulocytes from January 2014 till December 2015. This division is based on the change in our policy to use granulocytes within 48 h of septicemia as the incidence of drug resistant bacterial strains had increased. We analyzed the underlying conditions, the indications and associated complications. Outcome was measured in terms of efficacy in tiding over the current septic episode for which granulocyte transfusion was used.

Peripheral granulocyte mobilization was achieved with either single dose injection GCSF 5 mcg/kg or single dose oral Dexamethasone 8 mg taken the night before.

Granulocyte transfusion starts with appropriate donor selection. At our institute, we follow strict donor standards as mentioned subsequently. Donors were blood group compatible, negative for viral screen and in good general condition. All the donors were voluntary donors recruited by the family of affected children or those that were already registered and screened for platelet donation. Written informed consent was obtained from all donors. We avoided multiparous women in view of increased risk of alloimmunization. In case of ABO incompatible hematopoietic stem cell transplant recipients we had used O positive donors.

Pre-transfusion testing for the donor included a complete haemogram and viral screening which included Nucleic acid testing (NAT). All donors had transient generalized myalgia for approximately 12–24 h post GCSF injection and transient perioral tingling and numbness during the apheresis process. There were no other significant donor adverse events.

1 unit of granulocyte apheresis products contained approximately 1×10^9 granulocytes per milliliter. The granulocytes collected were irradiated with 25 Gy to prevent transfusion associated graft versus host disease transfused at a dose of 10 ml/kg of the child's body weight.

We follow the British Committee for Standards in Hematology (BCSH) guidelines as our transfusion policy. The Quality control parameters we applied were ensuring that each unit contained a minimum of 1×10^9 granulocytes per milliliter, that the unit was irradiated with 25 Gy

and that the infusion was given within 6 h of collection with adequate premedication.

Results

Data on 72 children with febrile neutropenia treated with 230 granulocyte infusions from January 2007 till December 2015 was analyzed. The first group included 48 children over a 6 years period from January 2007 to December 2013 and the second group had 24 from January 2014 to December 2015. The underlying conditions included hematopoietic stem cell transplant recipients ($n = 35$), leukaemia ($n = 33$), chronic granulomatous disease ($n = 1$), leukocyte adhesion defect ($n = 1$) and severe aplastic anemia ($n = 2$).

From 2007 to 2013 ($n = 48/72$) we had 27/48 (56 %) culture proven sepsis. Fourteen out of 27 children (51 %) were carbapenem resistant gram negative bacilli, Aspergillosis in 3, Burkholderia in 2, *Acinetobacter baumannii* in 2, *Pseudomonas aeruginosa* in 2 and 1 each with pansensitive gram negative bacilli—*Okrobacterium* species, *Chrysobacterium* species and H1N1. Of these 27, 11 children survived the septic episode (41 %).

In January 2013, we had changed our policy to transfuse granulocytes within 48 h of septic episodes as we noticed a rising trend in carbapenem resistant bacterial infections. From 2014 to 2015 ($n = 24/72$) 22 patients had culture proven sepsis (91 %) of which 20 had carbapenem resistant gram negative bacilli, 1 with Aspergillosis and 1 with Enterobacteriaceae species. 12/22 (54 %) with culture proven sepsis survived the episode. The survival rate had improved from 41 % in first group to 54 % after early intervention with granulocytes (P value is 0.0347) Relative risk = 0.6839 and 95 % CI 0.5068–0.9229. No adverse events were noted in any of the donors till date. None of the children had any significant complications post infusion of granulocytes.

Discussion

Granulocyte transfusions have been used for severe neutropenia with absolute neutrophil count <500 with associated severe infection not responsive to broad spectrum antibiotics and antifungals [1, 2]. They also have a role to play in children with neutrophil dysfunction with invasive aspergillosis and sepsis.

There have been no randomized controlled granulocyte transfusion trials in children, and most available data are derived from observational studies [3]. Sachs et al. reported a 92.6 % overall response rate to early granulocyte

transfusions. In this study, 25 of 27 patients with culture proven sepsis cleared their initial infection. All six patients with invasive Aspergillosis showed clinical and radiological improvement [4]. Another retrospective analysis in 2009 in 13 children with sepsis who received 14 courses of granulocytes reported a good short-term survival (12/14 courses, 86 %), although long-term outcome remained poor [5]. In 2011, Atay et al. [6] reported an overall survival of 77 % at day 30 post granulocyte transfusion in 35 children with febrile neutropenia or neutrophil dysfunction. We had previously published our data on granulocyte transfusions in children with neutropenic sepsis with 58 % children surviving the septic episode.

There are a few concerns regarding the safety of the use of granulocyte in extremely ill children. Transfusion associated lung injury (TRALI) and the risk of transmission of cytomegalovirus infections have been documented with granulocyte transfusions. All children at our centre were given premedication with antihistamines and antipyretics. Granulocytes were transfused within 6 h of collection with a maximum infusion time of 1 h. A minimal interval of 6 h needs to be maintained between granulocyte transfusion and infusion of Amphotericin B so as to prevent respiratory complications such as TRALI. No episodes of TRALI or anaphylaxis were reported in our series. A few studies have documented acute pulmonary reactions during infusion [7]. In a Cochrane meta-analysis, adverse events occurred in 15 % of the transfusions that had been collected by apheresis, but no reactions occurred in pre-medicated patients [8].

Cytomegalovirus infection (CMV) was documented in three children who underwent hematopoietic stem cell transplantation. Two out of three children had died subsequently due to resistant CMV disease. The immediate benefit of granulocyte transfusion has to be considered carefully in HSCT recipients as CMV reactivation is common after recovery from the neutropenic phase.

Indications for granulocyte transfusions in our series have shown a change over the last 8 years. From 2007 to 2013, indications were varied from children with primary immunodeficiency namely chronic granulomatous disease and sepsis among post transplant recipients and during AML and ALL induction. We have noted a significant change in the spectrum of organisms isolated, from gram negative bacilli, Aspergillosis and *A. baumannii* until 2013, to predominantly multidrug resistant gram negative organisms namely *Klebsiella pneumoniae*, *Escherichia coli* and *P. aeruginosa* from the start of 2014. This change is well documented in the present study in contrast to an earlier study by Raj et al. [9] in 2008 reporting 45 transfusions in 17 children, where maximum organisms isolated included *Candida albicans* and *Pseudomonas* species.

The timing of granulocyte transfusions has been shown to play an essential role in determining their efficacy. Survival chances are superior when transfusion is done early in the septic crisis particularly prior to onset of any end-organ damage. The early institution of granulocytes at our centre has facilitated statistically significant improved survival from 41 % till 2013 to 54 % from 2014 (*P* value is 0.0347). This however, was one of the interventions including early institution of colistin, an active infection control policy, surface cleaning and surveillance as per our hospital infection control team guidance.

Conclusions

Granulocyte transfusions are a safe and effective armamentarium in the supportive care required to tide over neutropenic sepsis. The indications for their use have shown a changing trend with increasing multidrug resistant organism sepsis. Early institution of granulocytes has helped improve survival from 41 to 55 % in culture proven sepsis. Clearly, this intervention cannot be taken in isolation. It goes in parallel to early use of appropriate antibiotics, an active hospital infection control policy and advances in pediatric intensive care. The above findings are a result of our experience with the use of granulocyte transfusions. A randomized control trial comparing the use of granulocytes with antibiotics and antibiotics alone needs to be explored for its feasibility and ethics.

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Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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