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Granulocyte transfusion experience in pediatric neutropenic fever: Splitted product can be an alternative?

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ABSTRACT

The granulocyte transfusion (GTX) has been used for a long time due to uncontrolled neutropenic fever with antimicrobial agents. In some cases, the product needs to be splitted for using in the next 12 hours. The aim of this study is to evaluate the efficacy of splitted product and clinical response to GTX.

In this study, 15 patients with malignancy with 19 neutropenic fever, who had received 56 GTX, were included. Seventeen of 56 GTX were splitted and used in maximum 12 hours during infections which did not respond to antibacterial and antifungal therapy in 7 days. The patients were divided in to response groups as a complete, partial and progressive. The predictive factors for response group were evaluated.

GTX were well tolerated in all patients. The median granulocyte dose was 1.26 (0.38–5.22) $\times 10^9$/kg. Total response rate was 89.5%. The infection-related mortality rate was 10.5%. Although the granulocyte doses are the same in both of the product groups, an hour later ANC increment of primer product was higher than that of splitted product ($p = 0.001$). Among the products, 48.7% of primer product and 17.6% of splitted product had induced $\geq 1000/mm^3$ ANC increment after an hour ($p = 0.039$).

Granulocyte transfusion is safe and effective in controlling the febrile neutropenia attack. GTX should be applied in a short time to provide effective ANC increment. For now, main granulocyte product instead of splitted product should be preferred in case of uncontrolled neutropenic fever with antibacterial/antifungal agents.

1. Introduction

Febrile neutropenia is a common emergency encountered in children receiving chemotherapy for malignancies. Left untreated, it can lead to serious morbidity and mortality. Febrile neutropenia is suspected in any patient on chemotherapy who presents with fever. Prompt evaluation and management is essential for a better outcome [1]. Initial stabilization, prompt initiation of appropriate antibiotics and adequate supportive care are the cornerstone of treatment [1]. Although broad-spectrum antibiotics and antifungal therapies had become the mainstay treatment of febrile neutropenia, they could not control infections in all cases and these patients require additional treatment strategies.

Granulocyte transfusion (GTX) is one of the supportive treatment modalities which has been used for a long time [2] The principle of GTX is harvesting donors with granulocyte colony-stimulating factor (G-CSF) and dexamethasone for acquiring sufficient dose of granulocyte [3]. The technology to yield granulocyte product had improved within

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recent years. However granulocyte concentration for children with low body weight, it is not always possible to use all of the GTX products. For this reason, granulocyte product may require splitting and might not be used immediately. The optimal dosage of granulocyte that can be given in terms of splitted product has not been well-known yet and the clinical benefits of GTX in febrile neutropenic patients in childhood period are still controversial.

In this study, we aimed to evaluate the clinical response to GTX in pediatric neutropenic fever and efficacy of splitted granulocyte product.

2. Materials and methods

2.1. Patients

A retrospective study design was planned to evaluate the granulocyte transfusions on the febrile neutropenic fever patients who were hospitalized at the pediatric hematology-oncology and infectious disease units of Dr. Behçet Uz Children's Hospital between the period of January 2013 to September 2014. Nine acute lymphoblastic leukemia (ALL), eight acute myeloid leukemia (AML), one hemophagocytic lymphohistiocytosis and one hepatoblastoma patients were enrolled. Data were collected from medical and computerized microbiology laboratory records of patients.

Neutropenia was defined as ANC < 500/mm^3 and fever was defined as a single oral or equivalent temperature of greater than 38.3 °C (101 °F) or two consecutive temperatures greater than 38.0 °C (100 °F) in a 12-hour period lasting at least 1 hour [4]. In our center, GTX treatment was initiated in cases whose fever did not recover despite 7 days of appropriate antibacterial and antifungal agents were applied GTX.

2.2. Donors

The donors were recruited by patients' family and they were admitted to the blood bank for screening. Approved donors had 8 mg of intravenous dexamethasone and 5 μ/kg G-CSF 12 hours before apheresis. Granulocyte donors were chosen according to CMV serology of patients. Donors ABO–Rhesus D were compatible with the patients and Kell negative. The written informed consent was obtained from all donors.

2.3. Granulocyte collection and transfusion

Granulocytes were collected with an automated apheresis system, Spectra Optia IDL (Terumo BCT) by the blood bank at Dr. Behcet Uz Children's Hospital. During granulocyte collection 6% Hetastarch [hydroxyethyl starch (HES)] was used to correct white blood cell sedimentation. Each granulocyte product was irradiated with 25 Gy before infusion. Seventeen products were in splitted two parts because of volume overload. The product was transfused as soon as possible and second the part of splitted products was transfused within 12 hours after collection which were called main and splitted product. Splitted products were preserved in room temperature. The patients were not given any premedication before GTX.

2.4. Evaluation of responses

The patients' blood samples were obtained at baseline, an hour and 24 hours after GTX to determine ANC. The patients were categorized according to their clinical response as complete if the patient had resolution of fever and physical examination findings within the 48-hour period, partial if the patient's clinical status did not meet criteria for complete response but there was improvement in patient's clinical status and progression if the patient had worsening clinical status or died [5]. Infection related death rate was calculated. Chills, fever and pulmonary symptoms were evaluated in terms of adverse reactions related with GTX.

2.5. Statistical analysis

The major outcomes studied were clinical response, 30 days mortality rate attributable to infections. Clinical responses and variables were compared using the Kruskal–Wallis test. The granulocyte product classified according to duration until transfusion and ANCs, transfusion dose per transfusion were compared using the Mann–Whitney U test. Correlation between neutropenia days with ANC < 500/mm^3 until GTX and transfusion count was evaluated with non-parametric Spearman test.

$P < 0.05$ was considered significant for all statistical tests. This study was approved by local ethics committee of the Dr. Behçet Uz Children's Hospital.

3. Results

Fifteen pediatric patients (M/F = 10/5) who fulfilled the criteria and treated with GTX were included in this study. Mean age of the patients were 9.3 ± 5.8 (1.0–16.0) years. A total of 56 GTX were given for 19 neutropenic fever episodes. Most patients were under intensive chemotherapy for ALL and AML (Table 1). The demographic features of the patients were reviewed in Table 1.

Among 56 GTX, 17 splitted products were given in maximum 12 hours after yielding. Granulocyte transfusion was applied daily for a median of 2 (range 1–7) days per episode. The median granulocyte content per transfusion was 1.26 (0.38–5.22) × 10^9/kg. The median ANC values of baseline, an hour and 24 hours after transfusion, were 200 (0–450)/mm^3, 1300 (100–8100)/mm^3 and 320 (0–2180)/mm^3 respectively. An hour and 24 hours after transfusion median values of ANC were higher than the median baseline value of ANC ($p = 0.001$ and $p = 0.002$ respectively). Also the median value of ANC measured after an hour of GTX treatment was higher than that of 24 baseline ANC ($p = 0.001$). The administered dose of granulocyte was correlated with granulocyte increment after an hour ($r = 0.362$, $p = 0.045$).

Probable factors that might be different between splitted and primer product were shown in Table 2. Only the ANC increase measured at the first hour after GTX treatment was significantly higher in patients who were treated with primer product instead of splitted product ($p = 0.001$). Also 48.7% of main product and 17.6% of splitted product had induced ANC increment of ≥1000/mm^3 after an hour ($p = 0.039$, Table 3).

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