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# Clinical outcomes and graft characteristics in pediatric hematopoietic stem cell transplantation: Effect of granulocyte-colony stimulating factor priming

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ABSTRACT

In this study, we aimed to determine the effect(s) of G-CSF priming on graft and transplantation parameters and compare these findings with those obtained without priming.

A total of 64 pediatric patients transplanted from HLA-matched family donors were enrolled in the study. Twenty-nine patients received G-CSF primed marrow (G-BM group) and 35 patients received steady state bone marrow (S-BM group). Number of total nucleated cells (TNC) and $CD34^+$ cells, CFU-GM colony number, neutrophil and platelet engraftment times, total length of stay in hospital, overall and disease free survival, and occasions of acute and chronic GvHD has been compared between these two groups.

Granulocyte colony stimulating factor primed bone marrow (G-BM) yielded higher numbers of $CD34^+$ cells, TNCs, and CFU-GM colony numbers compared to those obtained in S-BM. The neutrophil engraftment time, platelet engraftment time, length of stay in hospital, overall survival and disease free survival were not different between G-BM and S-BM groups. Also the cumulative incidence of grades II–IV acute and chronic GvHD were similar. It was observed that the use of G-CSF did not increase the risk of acute or chronic GvHD.

We concluded that use of G-CSF for stem cell mobilization is an effective and safe method in children.



## 1. Introduction

Hematopoietic stem cell transplantation from HLA-matched siblings significantly improved the long-term survival of the children with hematologic malignancies and bone marrow failure syndromes [1,2]. Traditionally, steady-state bone marrow (S-BM) has been used as the source of stem cells [3]. Granulocyte colony-stimulating factor (G-CSF) has been shown to promote hematopoietic progenitors and increase their numbers both in the bone marrow (BM) and in peripheral blood (PB) [4,5]. Thereafter, BM or PB stem cell (PBSC) transplantation after G-CSF mobilization has gained regard [3]. Results of clinical trials demonstrated that G-CSF primed PBSCs (G-PBSCs) offer the advantage of higher stem cell dose, accelerated engraftment and shorter neutropenic period compared with S-BM [6–11]. On the other hand, G-PBSCs has been associated with a higher risk of chronic graft vs. host disease (GvHD) due to higher numbers of T-cells, which may adversely affect quality of life as well as survival [12,13]. Studies concerning the use of G-CSF stimulated bone marrow (G-BM) revealed that it was safe and able to produce rapid engraftment as is the G-PBSCs [14–18]. Over and above, patients receiving G-BM appeared to have a lower incidence of chronic GvHD compared to those who received G-PBSCs [4].

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In this retrospective study, we compared clinical outcomes of children who had matched related hematopoietic stem cell transplantation (HSCT) by means of G-BM cells with those who were transplanted with S-BM cells.

## 2. Patients and methods

### 2.1. Patients

A total of 89 allogeneic stem cell transplantations were performed from HLA-matched family donor between April 2010 and November 2013 in our Institution's Bone Marrow Transplantation Unit and 64 patients, in which bone marrow was used as the stem cell source, were included in the study. Twenty-nine patients received the marrow grafts primed with G-CSF (G-BM group) and 35 patients received the steady state marrow (S-BM group). The numbers of total nucleated cells (TNC), and $CD34^+$ cells in the graft, CFU-GM colony number, neutrophil and platelet engraftment time, length of hospital stay, difference of weight between recipient and donor, acute or chronic GvHD, and other disorders occurred after HSCT, overall and disease free survival were evaluated respectively. Data have been compared between two groups. This retrospective study was approved by the institutional review board of the hospital (2013-072) and an informed consent was obtained after explanation of the procedure of bone marrow transplantation and bone marrow harvesting from all patients, donors, or their legal guardians.

### 2.2. Donor priming regimen and bone marrow harvesting

Steady state bone marrow was harvested from 35 donors (S-BM group) which weight was judged to fit recipient's need. Bone marrow priming was performed to 29 donors (G-BM group) when the weight of donor and recipient was discordant. Priming was performed in G-BM group with G-CSF (Biosimilar Filgrastim; Leucostim®, or Lenograstim; Granocyte®) at 10 μg/kg/day for 3 consecutive days, given as a single-dose subcutaneous injection. A targeted TNC number ($2–4 \times 10^8$/kg of recipient weight) was harvested on the 4th day from the posterior iliac crest under general anesthesia. The maximum safe volume collected was defined to be less than 20 mL/kg of donor weight. All grafts were evaluated for total volume, TNC number and the percentage of $CD34^+$ cell population. Total nucleated cell counts were obtained using an automated hemocytometer (LH 780 Hematology Analyzer, Beckman Coulter, Inc, USA). Number of $CD34^+$ cells were assessed by flow cytometry using standard monoclonal antibodies provided by the manufacturer (Navios Flow Cytometer, Beckmann Coulter, Inc, USA) as described elsewhere [2]. In vitro CFU-GM colony assay was determined by semisolid agar culture [19]. All the marrow infusions performed at day 0 without further manipulation.

### 2.3. Evaluation of engraftment

The time of neutrophil engraftment was considered as the first day of the 3 consecutive days with an absolute neutrophil count $\geq 0.5 \times 10^9$/L. The date of platelet engraftment was the first day of 7 consecutive days with a platelet count $\geq 20 \times 10^9$/L without transfusion.

### 2.4. Statistical analysis

Patient and graft characteristics, clinical outcomes (neutrophil engraftment, platelet engraftment, length of hospital stay) and peritransplant parameters (red cell and platelet transfusion requirement, days of total parenteral nutrition requirement) were compared between the G-BM and S-BM groups. Median values and ranges were calculated for the different variables. The distribution of variables was calculated by Kolmogrov–Smirnov test. Parametric variables compared with Student's t-test and for non-parametric variables, Mann–Whitney U-test or Kruskal–Wallis test were used. Non-categorical variables were compared with $\chi^2$ test. The cumulative probabilities of GvHD, overall survival and disease-free survival were calculated using the Kaplan–Meier methods and the log rank test. The date of the final analysis was December 3, 2013. Statistical analysis was performed by using Statistical Package for the Social Sciences for Windows (SPSS) version 18.0 (SPSS Inc., South Wacker Drive, Chicago, IL, USA).

## 3. Results

### 3.1. Donor characteristics

In the G-BM group there were 16 male (55.2%) and 13 female (44.8%) donors with a median age of 10 years (range: 1.2–50) whereas the S-BM group consisted of 13 male (37.1%) and 22 female (62.9%) donors with a median age of 11.5 years (range: 2–33.8, Table 1). The adverse effects of G-CSF injections were mild bone pain (n = 6, 20.6%), myalgia (n = 5, 17.2%), headache (n = 8, 27.5%), increase in lactate dehydrogenase (n = 9, 31%) and increase in alkaline phosphatase (n = 5, 17.2%) which were successfully treated with paracetamol. Although the median volume of harvest was larger in the S-BM group compared to those in G-BM group (480 mL vs. 729 mL), the difference was not significant (p = 0.243; Table 2). However, drop of hemoglobin level after harvest was significantly higher in donors of S-BM group (2.68 ± 0.96 gr/dL vs. 2.17 ± 0.86 gr/dL, p = 0.03). As well, the frequency of hypotensive periods during the harvesting procedure was higher in the S-BM group [n = 9 (25.7%) vs. n = 2 (6.9%)].

### 3.2. Patient characteristics

Clinical characteristics of recipients and donors are summarized in Table 1. There were 14 male (48.3%) and 15 female (51.7%) patients with a median age of 10.5 years (range: 1.8–16.5) in the G-BM group and 17 male (48.6%) and 18 female patients with a median age of 7 years (range: 1–16.3) in the S-BM group. Mean difference between weight of donor and recipient was smaller in G-BM group compared to those in S-BM group [4 ± 14.6 kg vs. 16.7 ± 14.9 kg, p = 0.001]. To better understand this, sub-groups were formed according to the donor's weight. In the G-BM group, there were 10 donors (34.5%) whose weights were below 20 kg, 7 donors (24.1%) whose weights were between 20 and 40 kg, 7 donors (24.1%) whose weights were between 40 and