Marginal Benefit/Disadvantage of Granulocyte Colony-Stimulating Factor Therapy After Autologous Blood Stem Cell Transplantation in Children: Results of a Prospective Randomized Trial

By Yoshifumi Kawano, Yoichi Takaue, Junichi Mimaya, Yasuo Horikoshi, Tsutomu Watanabe, Takanori Abe, Yukitoshi Shimizu, Takeji Matsushita, Atsushi Kikuta, Arata Watanabe, Asayuki Iwai, Etsuro Ito, Mikiya Endo, Nobuyuki Kodani, Shigeru Ohta, Kazuo Gushi, Hiroshi Azuma, Takao Etoh, Yasuhiro Okamoto, Koji Amano, Hiroyoshi Hattori, Haruhiko Eguchi, and Yasuhiro Kuroda for the Japanese Cooperative Study Group of PBSCT

In this prospective trial, a total of 74 children who were scheduled to undergo high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT) were prospectively randomized at diagnosis to evaluate the effectiveness of exogenous granulocyte colony-stimulating factor (G-CSF) treatment in accelerating hematopoietic recovery after PBSCT. The diagnosis included acute lymphoblastic leukemia (ALL) (n = 27), neuroblastoma (n = 29), and miscellaneous solid tumors (n = 18). Eligibility criteria included (1) primary PBSCT, (2) chemotherapy-responsive disease, and (3) collected cell number $>1 \times 10^5$ colony-forming unit–granulocyte-macrophage (CFU-GM)/kg and $>1 \times 10^6$ $CD34^+$ cells/kg patient's body weight. After applying the above criteria, 11 patients were excluded due to disease progression before PBSCT (n = 6) or a low number of harvested cells (n = 5), leaving 63 patients for analysis; 32 patients in the treatment group (300 $\mu g/m^2$ of G-CSF intravenously over 1 hour from day 1 of PBSCT) and 31 in the control group without treatment. Two distinct disease-oriented high-dose regimens without total body irradiation consisted of the MCVAC regimen using ranimustine (MCNU, 450 mg/m^2), cytosine arabinoside (16 g/m^2), etoposide (1.6 g/m^2), and cyclophosphamide (100 mg/kg) for patients with ALL, and the Hi-MEC regimen using melphalan (180 mg/m^2), etoposide (1.6 g/m^2), and carboplatinum (1.6 g/m^2) for those with solid tumors. Five patients (two in the treatment group and three in the control group) were subsequently removed due to protocol violations. All patients survived PBSCT. The median numbers of transfused mononuclear cells (MNC), $CD34^+$ cells, and CFU-GM were, respectively, 4.5 (range, 1 to 19) $\times 10^8$/kg, 8.0 (1.1 to 25) $\times 10^6$/kg, and 3.7 (1.2 to 23) $\times 10^5$/kg in the treatment group (n = 30) and 2.9 (0.8 to 21) $\times 10^8$/kg, 6.3 (1.1 to 34) $\times 10^6$/kg, and 5.5 (1.3 to 37) $\times 10^5$/kg, respectively, in the control group (n = 28), with no significant difference. After PBSCT, the time to achieve an absolute neutrophil count (ANC) of $>0.5 \times 10^9$/L in the treatment group was less than that in the control group (median, 11 *v* 12 days; the log-rank test, $P = .046$), although the last day of red blood cell (RBC) transfusion (day 11 *v* day 10) and the duration of febrile days (>38°C) after PBSCT (4 *v* 4 days) were identical in both groups. However, platelet recovery to $>20 \times 10^9$/L was significantly longer in treatment group than control group (26 *v* 16 days; $P = .009$) and $>50 \times 10^9$/L tended to take longer in the treatment group (29 *v* 26 days; $P = .126$), with significantly more platelet transfusion-dependent days (27 *v* 13 days; *t*-test, $P = .037$). When patients were divided into two different disease cohorts, ALL patients showed no difference in engraftment kinetics between the G-CSF treatment and control groups, while differences were seen in those with solid tumors. We concluded that the marginal clinical benefit of 1 day earlier recovery of granulocytes could be offset by the delayed recovery of platelets. We recommend that the routine application of costly G-CSF therapy in children undergoing PBSCT should be seriously reconsidered.

RECENTLY, SOME HEMATOPOIETIC growth factors have been used clinically in patients undergoing high-dose chemotherapy with hematopoietic stem cell transplantation, and their effects in ameliorating the neutropenic period have been reported.[1,2] High-dose chemoradiation therapy and autologous peripheral blood stem cell transplantation (PBSCT) has become an established option for the treatment of certain types of childhood cancer.[3] The popularity of PBSCT over bone marrow transplantation (BMT) is in part due to more rapid engraftment. As a result of data obtained in BMT studies, the use of growth factors, including granulocyte-colony stimulating factor (G-CSF), is widespread in PBSCT procedures, with the anticipation that hematopoietic recovery will be further accelerated.[4-15]

Although randomized studies with adult patients have reported accelerated hematopoietic recovery with the use of

From the Department of Pediatrics, University Hospital of Tokushima, Tokushima; Stem Cell Transplant Unit, National Cancer Center Hospital, Tokyo; the Department of Hematology/Oncology, Shizuoka Children's Hospital, Shizuoka; the Department of Pediatrics, University Hospital of Yamagata, Yamagata; the Department of Pediatrics, International Medical Center of Japan, Tokyo; the Department of Pediatrics, Fukushima Prefectural Medical College, Fukushima; the Department of Pediatrics, University Hospital of Akita, Akita; Kagawa Children's Hospital, Kagawa; the Department of Pediatrics University Hospital of Hirosaki, Aomori; the Department of Pediatrics, Iwate Medical University, Iwate; the Department of Pediatrics, Matsuyama Red Cross Hospital, Ehime; the Department of Pediatrics, Shiga Medical College, Shiga; the Department of Pediatrics, Naha Hospital, Okinawa; the Department of Pediatrics, Asahikawa Medical College, Hokkaido; the Department of Pediatric Surgery, Chiba Children's Hospital, Chiba; and the Department of Pediatrics, University of Kurume, Fukuoka, Japan.

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Address reprint requests to Yoichi Takaue, MD, Department of Medical Oncology, Hematopoietic Stem Cell Transplant Unit, National Cancer Center Hospital, 1-1 Tsukiji 5-Chome, Chuo-ku, Tokyo 104, Japan; e-mail: ytakaue@gan2.ncc.go.jp.

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G-CSF after PBSCT,[1,16] whether this actually provides any practical clinical benefit remains the subject of debate and needs further clarification. Routine use of G-CSF in children undergoing PBSCT should be seriously evaluated, because the stem cell kinetics, hematopoietic reservoir, and profile of the effects of G-CSF might be quite different from those in adult patients. Indeed, the results of our retrospective study with pediatric patients suggested that the clinical application of G-CSF after PBSCT did not have a significant clinical effect.[17]

We report here the first prospective randomized trial in children to determine whether engraftment after PBSCT is improved by the addition of exogenous G-CSF. The dose of infused stem cells should affect de novo engraftment speed. Hence, patients were randomized at diagnosis to either receive G-CSF or not, while those from whom a threshold number of cells could not be collected were excluded. The present results cast doubt on the benefit of G-CSF treatment in this special setting.

MATERIALS AND METHODS

Patients. From December 1993 to December 1996, 74 patients with various types of cancer were registered into our clinical protocol studies, as reviewed elsewhere.[18,19] The diagnosis included acute lymphoblastic leukemia (ALL) in complete remission (n = 27), neuroblastoma (n = 29), and miscellaneous solid tumors (n = 18). All of the patients with ALL and neuroblastoma were uniformly treated according to the protocols of the Japanese Cooperative Study Group of PBSCT. All of the patients with ALL were treated for more than 7 months with conventional chemotherapy and then prepared for PBSC collection. All received central nervous system (CNS) prophylaxis with a minimum of five courses of intrathecal administration of methotrexate (15 mg/m^2), cytosine arabinoside (Ara-C; 30 mg/m^2), and hydrocortisone (50 mg/m^2) at the completion of induction therapy and immediately before PBSCT. The initial chemotherapy for patients with other solid tumors varied at participating institutes, although they were similarly treated with regimens containing cyclophosphamide (CY), vincristine, pirarubicin (THP-ADR), etoposide (VP-16), dacarbazine (DTIC), cisplatinum or carboplatinum (CBDCA). Selected patients underwent delayed primary or second-look surgery and/or intraoperative radiation treatment (10 to 20 Gy).

To perform an intent-to-treat analysis, all of the patients were randomly assigned at the time of diagnosis into one of two groups: treatment group with G-CSF (300 μg/m^2) after PBSCT (n = 38) versus control group without G-CSF (n = 36). The registered patients proceeded to PBSCT when the following criteria were satisfied: (1) primary case of PBSCT, (2) chemotherapy-responsive disease, and (3) the numbers of collected cells exceeded 1×10^5 colony-forming unit–granulocyte-macrophage (CFU-GM)/kg and 1×10^6 CD34$^+$ cells/kg patient's body weight. The protocol was approved by the Institutional Review Board of each institute and consent was obtained from the patients' guardians.

Harvest of PBSCs. PBSCs were collected by apheresis in the recovery phase of marrow function after intensive chemotherapy with G-CSF (filgrastim; Kirin Brewery Co, Tokyo, Japan), as previously reported.[20-22] Briefly, the patients received 50 to 200 μg/m^2 of intravenous (IV) G-CSF from when white blood cell (WBC) count fell to 0.5×10^9/L after chemotherapy to the time of apheresis. When patients were judged to be in complete remission, PBSCs were harvested, and the criteria for performing apheresis included WBC of $>3.0 \times 10^9$/L and a platelet count of $>100 \times 10^9$/L. The regimens for mobilization chemotherapy were high-dose Ara-C (2 g/m^2 twice daily for 5 days) plus VP-16 (100 mg/m^2 for 3 days) for ALL, and the combination of THP-ADR (40 mg/m^2), CBDCA (400 mg/m^2), and VP-16 (100 mg/m^2 for 3 days) for solid tumors. The harvested cells were frozen with a nonprogrammed freezing method and stored in electric medical freezers set at −80°C or −135°C (Sanyo Electric Co, Tokyo, Japan) until use, as previously reported.[23]

Assay of CD34$^+$ cells. Assay of CD34$^+$ cells was exclusively performed by Ohtsuka Assay Institute (Tokyo, Japan) as a central laboratory. Sample cells were shipped by air cargo and assayed within 24 hours. Sample cells were adjusted to 1×10^6 cells/mL in Iscove's modified Dulbecco's Medium (IMDM; GIBCO-BRL, Life Technologies Inc, Grand Island, NY). Aliquots of 0.3 to 0.5 mL were then transferred in a volume of 1.5 mL of medium with 10% fetal bovine serum (FBS, Filtron PTY Ltd, Brooklyn, Australia) and stored at 4°C until analysis within 24 hours. A total of 100 μL of cell suspension was dispensed into a test tube (Falcon 2052; Becton Dickinson, Lincoln Park, NJ) for staining and for a control. Staining was performed in the test tube by adding phycoerythrin (PE)-conjugated CD34 antibody (anti-HPCA$_2$ antibody; Becton Dickinson) at a concentration of 1 μg antibodies/10^6 cells. PE-mouse IgG$_1$ was used as a control. After 30 minutes of incubation in the dark, cells were washed twice and resuspended in Dulbecco's phosphate-buffered solution (PBS; Nissui, Tokyo, Japan) containing 1% bovine serum albumin (BSA; Sigma, St Louis, MO; A-4503). In the case of substantial contamination of the sample with red blood cells (RBC), they were lysed with a solution consisting of 0.826% (wt/vol) NH_4CL, 0.1% $KHCO_3$, and 0.004% EDTA-4Na.

Samples were analyzed with a FACScan flow cytometer (Becton Dickinson). After function was verified, samples were drawn into the flow cytometer using forward scatter (FSC) and side scatter (SSC), as gating parameters along with debris subtraction techniques to determine the characteristics of the cells. A total of 20,000 events was counted to identify the mononuclear cell fraction. The flow cytometric data were analyzed using a gated analysis via a set of SSC-FL parameters for CD34$^+$ cells to calculate the percentage of positive cells.[24]

Assay of hematopoietic progenitor cells. Assays of hematopoietic progenitor cells using shipped frozen samples were principally performed at the University of Tokushima as a central laboratory, as previously described.[21] Briefly, cells were thawed using DNase (20 U/mL; Sigma, DN-25) containing medium and washed three times with PBS. Cells were then resuspended in IMDM for colony assay. Cells were incubated in methylcellulose cultures supplemented with 20% FBS, 450 μg/mL of human transferrin (Sigma T-1147), 2 U/mL of recombinant human erythropoietin (2×10^5 IU/mg protein, Kirin Brewery Co), 1% crystallized BSA (Calbiochem 12657; Hoechst Japan, Tokyo), and a combination of recombinant human G-CSF (Kirin), interleukin-3 (Kirin), and stem cell factor (Kirin). These factors were used at a final concentration of 20 ng/mL, which was the prescreened optimal concentration in our laboratory. Triplicate or quadruplicate cultures were plated in volumes of 0.4 mL in 24-well tissue culture plates (Corning 258201, New York, NY) and placed in an ESPEC N_2-O_2-CO_2 BNP-110 incubator (Tabai ESPEC Co, Osaka, Japan), which maintained 5% carbon dioxide, 5% oxygen, and 90% nitrogen in a humid atmosphere at 37°C. Plates were incubated for 14 days and colony-forming units for CFU-GM were counted using an inverted microscope.

Treatment regimens. As a cytoreductive therapy before transplant, the MCVAC regimen, consisting of ranimustine (MCNU, 450 mg/m^2), Ara-C (16 g/m^2), VP-16 (1,600 mg/m^2), and CY (100 mg/kg), was used for patients with ALL. Patients with solid tumors received a combination of melphalan (180 mg/m^2), VP-16 (1,600 mg/m^2), and CBDCA (1,600 mg/m^2). These protocols do not incorporate total body irradiation (TBI) and are considered marrow-ablative. Thirty-six hours after completion of the cytoreductive regimen, the cells were rapidly thawed at 37°C and promptly infused into the patients through a central venous catheter without additional postthaw washing manipulation. No further specific antileukemia or antitumor therapy was given after PBSCT. In

the treatment cohort, 300 μg/m^2 of G-CSF (filgrastim) were intravenously given to patients over 1 hour from the day after PBSCT (day 1) until the absolute neutrophil count (ANC) reached 3.0×10^9/L.

Supportive therapies. All of the patients had a central venous catheter and were kept in a protected environment, but with no oral decontamination. When patients developed fever or any evidence of infection, they were treated with broad-spectrum antibiotics either with or without intravenous γ-globulin preparations according to the guidelines of the individual institutes. RBC and platelet transfusions were performed to maintain levels of 7.0 g/dL and 20×10^9/L, respectively. Blood components were irradiated and filtered to reduce contaminating leukocytes.

Statistical analysis. Because all medical costs related to cancer therapy in pediatric patients are paid by the government in Japan, the duration of hospitalization is not a meaningful indicator of clinical benefit. Therefore, the primary end point of this study was the evaluation of engraftment speed. The day of hematopoietic recovery was defined as the first day with an ANC of at least 0.5×10^9/L, a platelet count of 20 or 50×10^9/L without transfusion for 3 consecutive days. The Mann-Whitney U-test and Student's *t*-test were used to analyze the effect of G-CSF administration. Kaplan-Meier estimates of time to ANC and platelet recovery were also analyzed using the log-rank test.

RESULTS

Patients. Eleven of the 74 registered patients did not proceed to PBSCT; six patients (three from each group) developed disease progression before blood cell harvesting. The other five patients (three from the treatment and two from the control group) were excluded because an inadequate number of cells was collected. Consequently, 63 patients (32 in the treatment group and 31 in the control group) were finally evaluated for the benefit of G-CSF after PBSCT. However, two cases in the treatment group who were administered the incorrect dose of G-CSF and three in the control group who were given G-CSF were excluded from the analysis because of protocol violations (Fig 1). The evaluated patients in both groups were comparable in terms of their clinical characteristics (Table 1) and the numbers of transfused cells (Table 2).

Transplant procedure and clinical parameters. All of the patients who underwent PBSCT showed little evidence of serious transplant-related complications. After PBSCT, the patients received G-CSF for a mean number of 15 days (range, 10 to 25), which resulted in an average cost of G-CSF of about $7,500 per person.

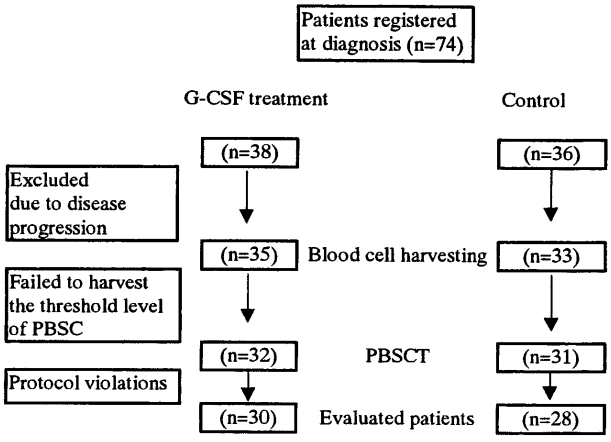

Fig 1. Schema of patient registration.

Table 1. Diagnosis and Characteristics of Registered Patients

	Treated Group	Control
Diagnosis		
ALL	13	15
NHL	3	1
Neuroblastoma	12	8
Brain tumors	2	2
Wilms' tumor	0	1
Yolk sac tumor	0	1
Age		
Median	6.4	6.8
Range	2-17	1-16
Sex		
Male	15	17
Female	15	11

Abbreviations: ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma.

In patients in the control group, the median number of days to achieve an ANC of 0.5×10^9/L was 12 (9 to 49), while it was 11 (8 to 20) in the treatment group. There was a significant difference between the two groups, with *P* values of .034 (*t*-test) and 0.046 (log-rank test). On the other hand, the median numbers of days to achieve platelet counts of 20 and 50×10^9/L in the control group were 16 (6 to 45) and 26 (11 to 100), respectively, whereas these were 22 (7 to 101) and 31 (13 to 123), respectively, in the treatment group. There was a statistically significant difference in early platelet recovery between the two groups (20×10^9/L: $P = .020$ by *t*-test and $P = .009$ by log-rank test). The results of a Kaplan-Meier analysis with a log-rank test are shown in Fig 2. Furthermore, the last day of platelet transfusions in the control group (day 13), occurred significantly sooner than that in the treatment group (day 27) ($P = .037$ by *t*-test). The numbers of days with febrile (>38°C) episodes (4 *v* 4) and the day of the last RBC transfusion (10 *v* 11) were comparable between the two groups (Table 3).

When patients with ALL and solid tumors were analyzed separately, the engraftment data in G-CSF–treated ALL patients were identical to those in control ALL patients. However, in patients with solid tumors, granulocyte engraftment occurred on days 11 and 12, respectively, and this difference was significant.

Table 2. Infused Number of Cells

	MNC ($\times 10^8$/kg)	CD34$^+$ ($\times 10^6$/kg)	CFU-GM ($\times 10^5$/kg)
Treated group			
G-CSF(+)	4.6	8.5	4.8
n = 30	(1-19)	(1.8-64)	(1.2-23)
Control			
G-CSF(−)	3.8	6.3	5.5
n = 28	(1.1-21)	(1.1-34)	(1.3-37)
P value			
t-test	.706	.571	.311
U-test	.643	.423	.247

Figures represent median value/(range).
Abbreviations: *t*-test, Student t-test; U-test, Mann-Whitney U-test.

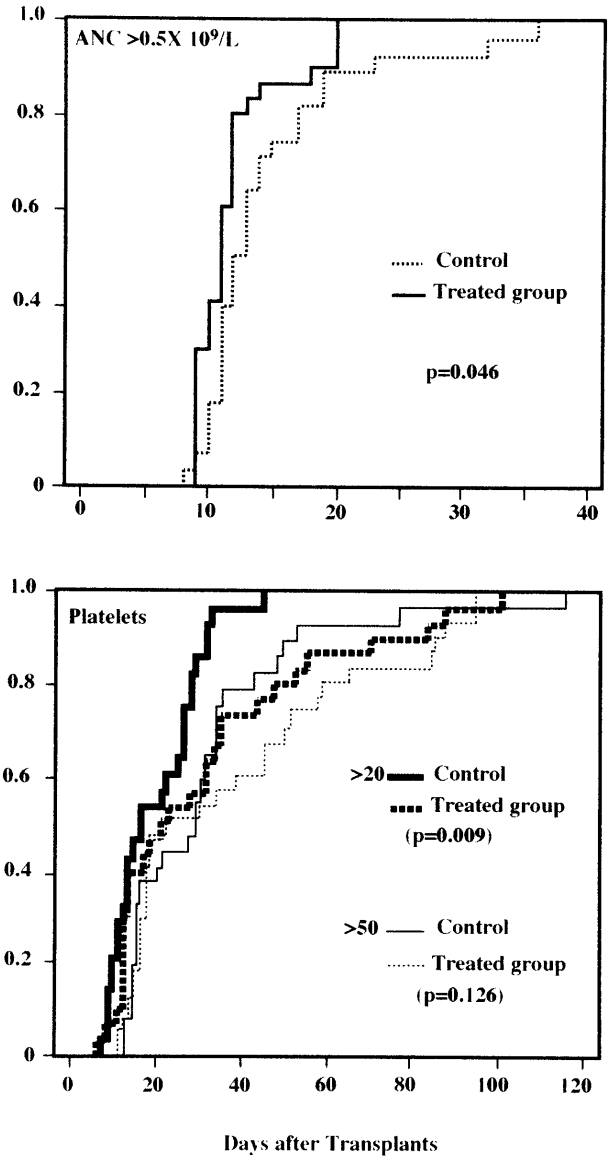

Fig 2. Kaplan-Meier probability of achieving 0.5 × 10⁹/L of ANC (top graph, *P* = .046), and those of 20 or 50 × 10⁹/L of platelet counts independent of platelet transfusions (bottom graph, *P* = .009 for 20 × 10⁹/L or *P* = .126 for 50 × 10⁹/L).

Although platelet engraftment tended to be delayed in the treatment group, this difference was not significant (Table 4).

DISCUSSION

Despite the widespread use of G-CSF after high-dose chemotherapy with stem cell support, there have been no comprehensive evaluations of the clinical benefit of this strategy after autologous PBSCT in pediatric patients. The presumed reason for the rapid hematopoietic recovery after PBSCT compared with BMT is the infusion of relatively more early engrafting committed progenitors.[25] We and others have previously suggested that the enhanced endogenous secretion of cytokines at least partly contributes to this early recovery.[26,27] The enhancement of hematopoietic recovery after autologous bone marrow transplantation (ABMT) by treatment with CSFs appears to be offset by the finding that further enhancement can be achieved with G-CSF–primed PBSC support without posttransplant CSF. The results of recent clinical studies on the value of G-CSF after PBSCT have been controversial, as summarized in Table 5.[1,2,4-16] We believe that the reported degree of effectiveness does not provide a practical clinical benefit.

Although we could not perform a critical cost analysis, which considered supportive therapy or hospitalization due to our government-supported insurance policy, G-CSF did not appear to provide any benefit when used after autologous PBSCT, although this result must be considered preliminary given the small number of patients studied. The reason for this marked contrast with adult studies remains unclear, but is most likely due to differences in the quantity and/or quality of PBSC in the grafts between the studies. In addition, we previously presented data suggesting that hematopoiesis is more active in pediatric than adult populations, and both the reconstituting potential and quantity of stem cells are superior in children.[28] The guidelines of the American Society of Clinical Oncology state that treatment with G-CSF is unnecessary in patients with neutropenia of short duration, while it may benefit those with prolonged neutropenia.[29] Our study excluded 7.4% of the initially targeted patients due to a small number of cells available for transplantation. These patients with less than the threshold level of PBSC might be suitable candidates for supplemental therapy with G-CSF after PBSCT.

In previous studies with adult patients, we found that hematopoietic recovery in control groups without G-CSF was

Table 3. Hematopoietic Recovery Data

	ANC (>0.5 × 10⁹/L)	WBC (>1.0 × 10⁹/L)	Platelets (>20 × 10⁹/L)	Platelets (>50 × 10⁹/L)	Last Day of Transfusions RBC	Last Day of Transfusions Platelets	Febrile Days (>38°C)
Treated group							
G-CSF(+)	11	11	22	31	11	27	4
n = 30	(8-20)	(8-20)	(7-101)	(13-123)	(0-81)	(6-91)	(0-15)
Control							
G-CSF(−)	12	11	16	26	10	13	4
n = 28	(9-49)	(9-29)	(6-45)	(11-100)	(2-69)	(5-82)	(0-11)
P value							
t-test	**.034**	.180	**.020**	.265	.231	**.037**	.577
U-test	**.021**	.199	.086	.455	.68	.077	.716

Figures represent median value/(range). Boldface type means the statistical significance ($P < .05$).

Table 4. Infused Number of Cells and Hematopoietic Recovery Data

	MNC ($\times 10^8$/kg)	CFU-GM ($\times 10^5$/kg)	CD34 ($\times 10^6$/kg)	WBC ($>1.0 \times 10^9$/L)	ANC ($>0.5 \times 10^9$/L)	Platelets ($>20 \times 10^9$/L)	Platelets ($>50 \times 10^9$/L)	Last Day of Transfusion RBC	Last Day of Transfusion Platelets	Febrile Days (>38°C)
ALL										
G-CSF(+)	5.1	5.0	15	11	12	13	16	10	13	3
n = 13	(1.3-11)	(1.5-23)	(2.4-23)	(8-20)	(9-20)	(12-88)	(13-92)	(0-81)	(6-85)	(0-14)
G-CSF(−)	3.3	6.9	6.3	12	12	12	16	8	12	4
n = 15	(1.1-11)	(2.2-37)	(1.1-29)	(9-25)	(9-49)	(8-45)	(11-100)	(4-41)	(5-40)	(0-10)
P value	.130	.399	.265	.695	.565	.107	.765	.908	.461	.908
Solid tumors										
G-CSF(+)	4.5	2.3	7.8	10	11	32	35	28	28	4
n = 15	(1.0-19)	(1.2-14)	(1.3-64)	(8-20)	(8-20)	(7-101)	(12-123)	(0-72)	(6-91)	(0-15)
G-CSF(−)	6.0	3.9	3.8	11	12	16	31	11	13	4
n = 13	(2.0-21)	(1.3-14)	(1.8-34)	(9-20)	(9-36)	(6-33)	(13-81)	(2-69)	(11-82)	(0-11)
P value	.403	.330	.559	.233	**.045**	.188	.630	.691	.143	.779

Figures represent median values/(ranges). Statistical significance was tested by the Mann-Whitney U-test.

generally slower than that in our clinical trials in a pediatric population. In the current study, the median time to an ANC $>0.5 \times 10^9$/L was 12 days in the control group, which was comparable to the results in G-CSF–treated groups in most of the adult reports. Panici et al[11] reported that platelet recovery to 50×10^9/L required about 11 days both in the control and treated groups. Because this speed of recovery was exceptionally fast compared with other studies, the cytoreductive regimen could not be considered myeloablative. In the data reported by Klumpp et al,[13] the infused dose of CFU-GM was $<1 \times 10^5$/kg, which was less than the widely accepted threshold for performing PBSCT with enhanced hematopoietic recovery. Thus, it is possible that G-CSF may be effective in a transplantation setting only with the use of fewer stem cells. On the other hand, Reiffers et al[30] reported that G-CSF had its greatest effect in the treatment of patients with acute myelogenous leukemia (AML). None of the patients in this study had AML, and this may explain the difference between the present results and those in previous studies.

The results in this study suggested that the use of G-CSF was associated with a delayed recovery of the platelet count after PBSCT. In patients who underwent autologous PBSCT, Bensinger et al[7] reported G-CSF tended to have an adverse effect on the time to platelet independence, but they failed to identify any statistically significant differences. In a multicenter retrospective survey involving 18 centers,[31] the use of posttransplant growth factors were associated with a longer time to platelet recovery in allogeneic marrow transplantations ($P = .01$). They speculated that the decreased probability of platelet recovery may be related to the reasons why growth factors were started rather than to a true biologic effect on recovery. In this prospective randomized study, we found a significant difference between the two groups both in the number of days to achieve a platelet count of 20×10^9/L ($P = .009$ by log-rank test) and the last day of platelet transfusion according to Student's *t*-test ($P = .034$). Although the exact cause of this result should be clarified, it is probable that G-CSF exerts negative effects via receptors expressed on platelets. The exposure of stem cells to a high concentration of G-CSF immediately after reinfusion may induce hematopoietic immature progenitor cells to myeloid

Table 5. Reports on the Benefit of Growth Factor Treatment After Autologous Stem Cell Transplantation

Author/ Reference	Type of Transplant	Study Design	Type of CFS	CSF-Treated Group ANC ($>0.5 \times 10^9$/L)	CSF-Treated Group Platelets ($>50 \times 10^9$/L)	Control Group ANC ($>0.5 \times 10^9$/L)	Control Group Platelets ($>50 \times 10^9$/L)	Benefit	Year of Report
Advani[2]	BCT	RMT	GM-CSF	12	NS	16	NS	Yes	1992
Shimazaki[6]	BCT	non-RMT	G-CSF	10	11	14	13	Yes	1994
Vey[4]	BMT	non-RMT	G-CSF	12	23/18*	16	21*	Yes	1994
Bensinger[7]	BCT	non-RMT	G-CSF	12	10*	NS	NS	Yes	1994
Spitzer[5]	BCT	RMT	G + GM-CSF	10	16	16	14	Yes	1994
Stahel[1]	BMT	RMT	G-CSF	10	NS	18	NS	Yes	1994
Brice[8]	BCT	non-RMT	G-CSF	10	17	17	17	Yes	1994
Dunlop[9]	BCT	non-RMT	G-CSF	11.2	21.9†	12.9	16.8†	No	1994
Cortelazzo[10]	BCT	non-RMT	G-CSF	10	14	12	16	No	1995
Klumpp[13]	BCT	RMT	G-CSF	11	19.5	17	20	Yes	1995
Panici[11]	BCT	non-RMT	G + Epo/GM + Epo	11	11.5	8/10	8/11	Yes	1997
McQuaker[16]	BCT	RMT	G-CSF	10	14.5	14	17	Yes	1997
Legros[12]	BCT	RMT	GM-CSF	12	13*	14	13*	No	1997
Tarella[14]	BCT	non-RMT	G-CSF	10	14	14	13	Yes	1998
Lee[15]	BCT	RMT	G-CSF	9.7	NS	13.2	NS	Yes	1998

Abbreviations: BCT, blood cell transplantation; RMT, randomized trial; Epo, erythropoietin; NS, data not shown.

* and † indicate that platelet recovery was the day on which a value of 20 and 15×10^9/L, respectively, was achieved.

committed progenitor cells, which results in the delayed growth of megakaryocyte progenitors or platelets. Further investigations on this point are required.

In conclusion, we showed that the use of G-CSF does not provide a marked clinical benefit in pediatric patients undergoing autologous PBSCT with more than a threshold level of PBSC, while this expensive strategy appears to be associated with a tendency for the delayed recovery of platelets. The benefit of G-CSF therapy, in terms of enhancing hematopoietic recovery after high-dose therapy, is more clearly indicated in our patient population in the setting of mobilization of PBSC.

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