Granulocyte Colony-Stimulating Factor "Mobilized" Peripheral Blood Progenitor Cells Accelerate Granulocyte and Platelet Recovery After High-Dose Chemotherapy

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Hematopoietic growth factors have been used to accelerate engraftment after bone marrow transplantation and to "mobilize" peripheral blood progenitor cells (PBPC). We report on the data in 85 consecutive patients with Hodgkin's disease who were treated in a single institution using different methods to obtain PB progenitor cells. Use of granulocyte colony-stimulating factor for mobilization resulted in a significantly accelerated time to recovery of granulocytes (10 days *v* 12 days, $P < .01$) when compared with "nonmobilized" PBPC recipients. Similarly, use of mobilized PBPC resulted in a significantly accelerated time to platelet engraftment (13 days *v* 30 days, $P < .001$) when compared with "nonmobilized" recipients. Moreover, there was a statistically significant difference in total costs in favor of the group receiving "mobilized" PBPC.

HEMATOPOIETIC growth factors were initially identified by their ability to support progenitor cells in culture assays.[1,2] Many such growth factors have since been cloned and investigated in a variety of clinical settings. Studies using granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage CSF (GM-CSF) after bone marrow transplantation (BMT) have demonstrated accelerated myeloid recovery compared with placebo-treated patients.[3-8] To date, no effect on platelet recovery was observed in these clinical trials, although GM-CSF has been demonstrated in vitro to enhance megakaryopoiesis.[9,10]

Our initial experience suggested that patients receiving peripheral blood progenitor cells (PBPC) had a more rapid recovery of granulocytes compared with those patients receiving BM only; however, no effect on erythroid and megakaryocytic lineages was seen.[6] Several investigators have attempted to increase the number of PBPC by "mobilizing" or "priming" the BM with chemotherapy and/or growth factors such as GM-CSF or G-CSF.[11-15]

We report on the engraftment data using different methods to obtain PBPC in 85 consecutive adult patients with Hodgkin's disease (HD) treated at Stanford University Medical Center using three preparative regimens and supportive care measures. Use of G-CSF for mobilization resulted in a significantly accelerated time to recovery of the granulocytes and platelets. A cost-benefit analysis showed a dramatic decrease in hospital costs associated with G-CSF "mobilized" PBPC primarily due to early discharge from the hospital and decreased transfusion requirements.

PATIENTS AND METHODS

Informed consent. All clinical protocols were approved by the Institutional Review Board at Stanford University Medical Center. The potential risks and benefits were explained to each patient in detail during at least two outpatient visits and again on the day of admission for BMT. Written consent was obtained for all trial participants.

Patients. From January 1988 through July 1991, 85 patients with relapsed HD received an autologous BMT. Patient characteristics are described in Table 1. All patients received PBPC with or without additional BM infusion. Five patients were excluded from the analyses: one patient received BM only because an apheresis catheter could not be placed, and four patients received cyclophosphamide and G-CSF for PBPC "mobilization." The rationale for using PBPC alone was BM involvement with HD or prior pelvic irradiation limiting the ability to harvest the BM. Most patients had at least two different combination chemotherapy regimens before the initiation of BMT.

Beginning in September 1989, patients participated in ongoing trials using different CSFs. Four sequential groups of patients were identified. Group I received no growth factor during the collection of PBPC or after the infusion of PBPC. Groups II and III received no growth factor during the collection of PBPC, but did receive GM-CSF (group II) or G-CSF (group III) after BMT. Group IV received G-CSF for mobilization of PBPC and again after infusion of BM and/or PBPC.

Apheresis and storage. A 12 French double lumen Hickman type catheter (Cook, Bloomington, IN) was placed before apheresis. Apheresis was performed using a Cobe Spectra (Cobe, Denver, CO) and 10,000 mL of blood volume was processed during each collection procedure. Platelet counts were maintained above 30,000/μL during the days of apheresis by transfusion of platelet concentrates irradiated with 2,500 cGy. In patients undergoing collection of "mobilized" PBPC, G-CSF (CTEP, NIH; or Amgen, Thousand Oaks, CA) was administered at a concentration of 10 μg/kg/d, administered intravenously (IV) or subcutaneously (SC) 4 days before initiation of apheresis and continued daily until the PBPC collection was completed. If the white blood cell count (WBC) exceeded 60,000/μL, G-CSF was held until the WBC decreased below 60,000/μL. Apheresis continued daily until the target cell dose of 10^9 mononuclear cells/kg was collected. Each collection of PBPC was frozen in a controlled-rate freezer (Cryomed, New Baltimore, MI) at a rate of $-1°C$ per minute to a temperature of $-50°C$ and at $-10°C$ per minute to a temperature of $-70°C$ and then transferred to the liquid phase of a liquid nitrogen freezer.

Colony assays and flow cytometry. Aliquots (1 mL) of the collections from each patient were thawed and pooled. Mononuclear cells were suspended in Iscove's modified Dulbecco medium with 20% fetal calf serum and 50 mmol 2-β mercaptoethanol in 1.1% methylcellulose for viscous support, using 17% human placental-conditioned medium as a source of CSF, as previously described.[16] The mononuclear cells were plated at a final concentration of 4×10^5 cells/mL in Costar Mark II tissue culture plates (24 to 16 mm

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Table 1. Patient Characteristics

	Group			
	I (—/—)	II (—/GM-CSF)	III (—/G-CSF)	IV (G-CSF/G-CSF)
No. of patients	32	21	7	20
Median age (yr) (range)	28 (14-49)	33 (18-49)	33 (18-41)	27 (15-48)
Sex				
Male	16	13	4	12
Female	16	8	3	8
No. of prior combination chemotherapy regimens				
1	6	5	4	5
≥2	26	16	3	15
BM involvement				
Yes	6	8	5	6
No	26	13	2	14
Status at time of BMT				
"Sensitive" relapse	25	15	6	16
"Resistant" relapse	7	3	0	4
Induction failure	—	3	1	—
Preparative regimen				
FTBI/VP-16/CY	9	5	2	1
BCNU/VP-16/CY	22	14	3	17
CCNU/VP-16/CY	1	2	2	2

diameter microtitre wells; Costar Corp, Cambridge, MA) in a final volume of 0.25 mL. Myeloid colonies were counted after 10 days of incubation at 37°C in a humidified incubator containing room air with 5% CO_2.

Cells expressing the surface marker CD34 were identified by indirect immunofluorescence with the monoclonal antibody My10 (Becton Dickinson, Mountain View, CA) and fluorescein isothiocyanate (FITC)-conjugated $F(ab')_2$ goat antimouse Ig reagent using a FACSTAR cell sorter (Becton Dickinson) as described previously.[17]

Preparative regimen and supportive care. Seventy-three patients received a preparatory regimen consisting of etoposide (60 mg/kg) IV over 4 hours on day −4 and cyclophosphamide (100 mg/kg) over 2 hours on day −2 with either fractionated total body irradiation (1,200 cGy) delivered from day −8 through day −5 or carmustine (BCNU; 15 mg/kg) IV over 2 hours on day −6. Seven patients with compromised respiratory function received pomustine (CCNU; 6 to 12 mg/kg) orally as part of a phase I-II dose escalation study on day −6 in place of the BCNU. At the time of autologous BM and/or PBPC administration (day 0), each bag was rapidly thawed in a 37°C water bath and infused through a large-bore central venous catheter over 5 to 10 minutes. Patients received GM-CSF (250 mg/m^2/d) or G-CSF (10 μg/kg/d) beginning on day +1. All patients were housed in private rooms with a high-efficiency particulate air filtration system. Reverse isolation techniques with masks and gowns were used when neutrophil counts decreased below 500/μL. Vancomycin (1 g IV every 12 hours) was initiated on the first day of neutropenia and broad spectrum antibiotics were used for the first febrile episode. All patients received prophylactic low-dose amphotericin (0.15 mg/kg) starting on day +1. All blood products were irradiated with 2,500 cGy. Platelets were transfused if the platelet count decreased below 20,000/μL. Leukocyte-depleted platelets were not used either before or during BMT, unless specifically indicated.

Statistical analysis. The statistical analysis was performed by the Mann-Whitney test.

RESULTS

Apheresis data. The median numbers of apheresis procedures required to obtain 10^9 mononuclear cells/kg in patients not receiving G-CSF was 9, with a minimum of 7 and a maximum of 14 (Table 2). Patients receiving G-CSF for the collection of PBPC required a median of only 4 (range, 2 to 11) procedures to achieve the same target number of PBPC. There were no clear differences in the collection of PBPC or outcome if the patients received G-CSF IV or SC. The median number of colony-forming units granulocyte-macrophage (CFU-GM) × 10^4/kg infused was higher in the group receiving G-CSF for the apheresis procedures compared with the groups not receiving G-CSF. Moreover, there were no detectable CD34$^+$ cells in the PB of the patients undergoing apheresis without G-CSF priming. The range of CD34$^+$ cells for patients who received G-CSF during the apheresis time was 0 to 57 cells/μL, with a median count of 9 cells/μL.

Engraftment. There was a statistically significant difference in the time to myeloid engraftment for the group receiving G-CSF "mobilized" PBPC and G-CSF after BMT (group IV) when compared with the groups receiving "nonmobilized" PBPC and either GM-CSF or G-CSF (groups II and III) after BMT (10 days *v* 12 days, $P < .01$). Patients who received G-CSF "mobilized" PBPC engrafted within a narrow range of time compared with those who did not receive "mobilized" PBPC (Table 2).

There was a statistically significant difference ($P < .001$) in time to stable platelet engraftment defined as a platelet count greater than 20,000/μL without the need for further platelet transfusions. The group receiving "mobilized" PBPC had a surprisingly rapid recovery of their platelet counts, with a median of only 13 days compared with 30 days in the "nonmobilized" groups. There was also a highly significant difference in median day of discharge ($P < .001$), favoring patients who received "mobilized" PBPC.

Toxicity. Two of the patients receiving G-CSF before apheresis each had one dose held because of a WBC in excess

Table 2. Treatment Data and Outcome

	Group			
	I (—/—)	II (—/GM-CSF)	III (—/G-CSF)	IV (G-CSF/G-CSF)
No. of patients	32	21	7	20
Median no. of apheresis (range)	9 (7-14)	8 (7-11)	8 (6-12)	4 (2-11)
Median no. of PBPC $\times 10^8$/kg infused (range)	10.9 (8-16)	10.9 (9-14)	10.4 (9-12)	10.7 (9-16)
Median no. of CFU-GM $\times 10^4$/kg infused (range)	4.4 (0-11)	4.2 (0-15)	4.0 (0-9)	9.4 (0-48)
Median number of $CD34^+$ cells collected/mL (range)	ND	ND	0	9 (0-57)
Median days to neutrophils >500/μL (range)	15 (9-86)	12 (9-21)	12 (9-44)	10 (7-14)
Median days to platelets >20,000/μL (range)	30 (4->365)	33 (11-283)	18 (6-83)	13 (7-39)
Median no. of single donor platelet transfusions (range)	20 (2->403)	15 (5-45)	14 (2-45)	5 (1-17)
Median days to discharge after BMT (range)	24 (16-47)	23 (14-37)	22 (16-36)	15 (10-21)

Abbreviation: ND, not done.

of 60,000/μL. Bony pains, especially in the sternum, were observed in two patients, but did not require any dose adjustment and resolved with analgesic therapy. No other untoward side effects were encountered.

Cost analysis. We conducted a cost-benefit analysis using short-term, direct medical costs associated with "mobilized" PBPC and G-CSF after BMT (Table 3). Outcomes were evaluated by segmenting the patients by time of G-CSF dose. The two groups compared were III and IV, so that the only variable was the use of G-CSF for mobilization of PBPC. Although the groups were not randomized, the two groups were treated concurrently and some of the patients participated in a randomized trial that was reported previously.[18] There was on the average a 45% net decrease in the major costs associated with BMT with the use of G-CSF "mobilized" PBPC. The majority of the cost savings were secondary to early platelet engraftment and earlier discharge from hospital.

DISCUSSION

Autologous BMT has been used in a wide variety of malignant diseases, including leukemia, lymphoma, neuroblastoma, and carcinoma of the breast.[19-23] There are multiple factors which affect the outcome of transplantation, such as the number of cells transplanted, the period of aplasia and other coincident morbidity resulting from infection or bleeding. Regardless of the transplantation technique used, however, the initial morbidity and mortality depends primarily on the incidence of bleeding and infection secondary to the period of aplasia after transplantation. If the period of granulocytopenia and thrombocytopenia can be shortened, the morbidity of bone marrow transplantation may be reduced and the total time in the hospital may be shortened. Both G- and GM-CSF have been used to accelerate hematopoietic reconstitution following high dose therapy and autologous BMT. These studies have demonstrated an accelerated recovery of the total white cell count as well as granulocyte count recovery.[3-8] However, so far, no impact on platelet recovery has yet been demonstrated.

Human PBPC can be collected following established techniques for platelet apheresis.[24] Recent experience has established the use of peripheral blood mononuclear cells as a source of pluripotent cells to reconstitute patients following ablative treatment.[6] We and others have observed more rapid engraftment with PBPC.[6,15,20] Methods to improve the col-

Table 3. Mean and Median Difference in Hospital Costs Between "Mobilized" PBPC and "Nonmobilized" PBPC

	—/G-CSF	G-CSF/G-CSF	Difference			
			Mean	% Change	Median	% Change
Costs						
Cost for G-CSF (for mobilization)	0	1,960	−1,960	NA	−1,904	NA
Benefits						
Apheresis costs	8,781	4,649	4,132	−45.7	4,132	−47.1
Platelet costs*	15,750	2,625	17,325	−82.5	13,125	−83.3
Room costs	17,274	9,618	7,541	−44.1	7,656	−44.3
Antibiotic costs	3,609	1,922	1,697	−44.9	1,687	−46.7

Abbreviation: NA, not applicable.

* Includes all platelet transfusions, including outpatient period.

lection of pluripotent progenitor cells have been investigated. At the time of leukocyte recovery following cytoreductive chemotherapy, there is a rebound in the number of CFU-GM colonies. Several investigators have attempted to increase the number of peripheral progenitor cells by mobilizing the progenitor cells from the marrow using either high dose chemotherapy or growth factors such as G-CSF or GM-CSF.[11-14] Recent evidence suggests that there is accelerated platelet engraftment with the use of G-CSF for mobilization of PBPC.[15,25]

We have analyzed 80 patients who received BMT for HD. All patients received PBPC. The median number of mononuclear cells collected was similar in all groups (Table 2). The number of CFU-GM infused was increased in the patients receiving "mobilized" PBPC. There was an increase in the number of $CD34^+$ cells collected with the use of G-CSF for "mobilization." Although these four groups do not represent prospective randomized patients, all patients had the same diagnosis, and the four groups were comparable in the number of prior cycles of chemotherapy, disease status, age, sex, BM involvement, and preparative regimens. Supportive care after BMT was identical in all patients.

There was a significantly shorter time to granulocyte engraftment if GM-CSF or G-CSF was used after BMT, as evidenced in the comparison between group I and groups II and III ($P < .01$). There were no differences in the engraftment times between groups II and III. No difference in the times to platelet engraftment was demonstrated between groups I, II, and III (P = NS). There was a statistically significant difference ($P < .01$) in the time to granulocyte recovery when patients received G-CSF "mobilized" PBPC and G-CSF (group IV) compared with patients receiving "nonmobilized" PBPC and either GM-CSF or G-CSF (groups II and III). More interestingly, a marked effect is found in the time to platelet recovery ($P < .001$) with earlier engraftment seen in group IV. Duration of hospital stay was also significantly reduced in patients in group IV ($P < .01$).

Moreover, our findings demonstrate that the use of G-CSF to augment the circulating pool of progenitor cells resulted in a lower number of apheresis procedures needed and a higher number of early hematopoietic precursors harvested. The fewer number of collections translated into a lower total actual cost for PBPC collection and the more rapid engraftment and earlier discharge resulted in a lower overall hospital cost (Table 3). The markedly decreased number of platelet transfusions necessary results in less exposure to heterologous blood products for the patient, a smaller chance of alloimmunization, and a significantly decreased financial cost ($P < .01$).

Use of G-CSF for "mobilization" increased the number of PBPC; however, the observation of a more rapid return of platelets was intriguing because G-CSF is not known to stimulate megakaryocytes in vitro or in vivo.[3,9] G-CSF is known to stimulate multilineage hematopoietic progenitors, but usually only in culture systems in which other CSFs are supplied by "contaminating" accessory cells.[26,27] One possibility may be related to shedding of adhesion molecules on the primitive multilineage cells with exposure to the growth factor, therefore allowing them to circulate. Similarly, another mechanism may be that the use of G-CSF for "mobilization" allows the growth factor to interact with other endogenous cytokines to release a population of more primitive hematopoietic progenitors into the PB that differentiate after myeloablative chemotherapy. Clearly, $CD34^+$ cells are found (although not always) after mobilization with G-CSF, whereas PBPC collected without "mobilization" were devoid of measurable $CD34^+$ cells.

The exact pathways for the stimulation of platelet recovery are still unknown at this time, but the observed engraftment appears stable and sustained. There is continued concern that use of "mobilized" PBPC may result in compromised durability of engraftment compared with BM graft recipients. However, we have not encountered any case of PBPC "exhaustion." Finally, this study did not address whether there is the need to use G-CSF after the infusion of G-CSF–primed progenitor cells. We are currently investigating the possible presence of more primitive progenitor cells in these collections by FACS analysis of early progenitor cell surface markers. Use of G-CSF "mobilized" progenitor cells appears to be very useful for early myeloid and platelet recovery, shortened hospitalization, and decreased costs.

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