Granulocyte Colony-Stimulating Factor After Allogeneic Bone Marrow Transplantation

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Hematopoietic growth factors have been shown to be effective in reducing the period of neutropenia after autologous bone marrow transplantation (BMT). Initial concerns over potential aggravation of graft-versus-host disease (GVHD) and increase in the incidence of relapse in patients with myeloid leukemias influenced the number of studies using hematopoietic growth factors after allogeneic BMT. We report the experience with 50 patients treated at a single institution using granulocyte colony-stimulating factor (G-CSF) after allogeneic sibling (n = 30) and matched unrelated (n = 20) BMT. The time to an absolute neutrophil count ≥500/μL was significantly faster in patients who received G-CSF and cyclosporine and prednisone for GVHD prophylaxis when compared with historical control patients receiving the same GVHD prophylaxis (10 *v* 13 days, *P* < .01). A similar accelerated myeloid engraftment was observed for those patients who received the addition of methotrexate for GVHD prophylaxis when compared with historical control patients receiving the same GVHD prophylaxis regimen (16 *v* 19 days, *P* < .05). The median time to engraftment for patients receiving a matched unrelated BMT and G-CSF was 17 days (range 13 to 26). We did not observe any increase in GVHD or early mortality in the matched related sibling BMT. The incidence of acute GVHD in the matched unrelated BMT recipients was also low at 21%; however, 9 patients (45%) died within 100 days of the date of BMT, similar to the experience reported with granulocyte-macrophage CSF. This study confirms the efficacy of G-CSF in accelerating myeloid engraftment after allogeneic matched sibling BMT. The higher early mortality associated with patients receiving matched unrelated BMT suggests that randomized controlled trials using G-CSF after allogeneic BMT should be performed.

HEMATOPOIETIC growth factors have been studied extensively after high-dose myeloablative therapy followed by autologous bone marrow transplant (ABMT). Granulocyte-macrophage colony stimulating factor (GM-CSF) has been shown in several phase III trials to accelerate neutrophil engraftment and reduce the number of infectious episodes after ABMT.[1-4] Granulocyte colony-stimulating factor (G-CSF) has also been shown to be effective in reducing the period of neutropenia after ABMT.[5-7]

Initial concerns over potential aggravation of graft-versus-host disease (GVHD) and increase in the incidence of relapse in patients treated for myeloid leukemias influenced the number of studies using hematopoietic growth factors after allogeneic BMT. Recent phase I-II trials using GM-CSF after allogeneic sibling BMT have shown earlier myeloid recovery with no increase in GVHD or relapse rates.[8] These results have been confirmed in phase III trials.[9-11]

There is less information available regarding the efficacy and safety of growth factors after matched unrelated BMT. One phase II trial examined the efficacy of GM-CSF after allogeneic BMT using unrelated donors.[12] No clear effect on myeloid recovery was shown relative to historical controls. GM-CSF was well tolerated and no adverse effects including incidence and severity of GVHD were noted. The results of a phase III trial using GM-CSF after matched unrelated BMT were recently presented.[13] The time to myeloid engraftment was shortened with GM-CSF without an increase in the incidence or severity of GVHD or the incidence of relapse. Of concern was a nonsignificant trend to less favorable 100-day and 1-year survival in the GM-CSF-treated group. Two previous studies examine the efficacy of G-CSF after allogeneic sibling BMT.[14,15] These phase I-II trials showed that G-CSF may accelerate myeloid recovery without evidence of increased toxicity from GVHD or relapse. There are currently no published trials using G-CSF after matched unrelated BMT.

We now report our experience in 50 patients treated at a single institution using G-CSF after allogeneic sibling (n = 30) and matched unrelated BMT (n = 20). Our trial confirms the efficacy of G-CSF in accelerating myeloid engraftment after allogeneic sibling BMT without an increase in incidence or severity of GVHD or relapse. We noted a higher-than-expected early mortality in patients treated with G-CSF after matched unrelated BMT. These data suggest that the use of G-CSF after allogeneic BMT should be tested in a randomized controlled clinical trial.

METHODS

Patients. From April 1992 until June 1993, 50 adult patients underwent allogeneic BMT at Stanford University Medical Center. Patient characteristics are shown in Table 1. Thirty patients received BM from HLA matched sibling donors. Fourteen had acute myelogenous leukemia (AML), nine chronic myelogenous leukemia (CML), three acute lymphoblastic lymphoma (ALL) and two each had aplastic anemia or non-Hodgkin's lymphoma (NHL). Eighteen patients with AML (n = 5) or ALL (n = 1) in first complete remission (CR), CML (n = 8) in chronic phase (CP), aplastic anemia (n = 2), or NHL (n = 2) were classified as good risk. The remaining 12 patients were considered poorer risk. Eight of the 12 had AML, 3 with induction failure (IF), 2 in first relapse, 2 with secondary AML, and 1 in second CR. The remaining 4 patients had relapsed (n = 3) or second CR ALL. The median age was 34 years with a range of 18 to 56. Twenty patients had matched unrelated donor transplants. Of these, 15 had CML (14 CP, 1 accelerated phase), 3 ALL (second CR, fourth CR, relapse), and 2 AML (1 IF, 1 secondary). Fourteen

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Table 1. Patient Characteristics

	Matched Sibling BMT With G-CSF (n = 30)	Matched Sibling BMT Controls (n = 52)	Unrelated Donor BMT With G-CSF (n = 20)
Median age in yrs (range)	34 (18-56)	30 (18-48)	42 (24-48)
Disease			
AML	14	18	2
CML	9	21	15
ALL	3	13	3
Other*	4	—	—
Disease status			
CR1/CP1	18	52	14
>CR1/CP1	12	—	6
GVHD prophylaxis			
CSA/PSE	13	25	0
CSA/MTX/PSE	17	27	20
Preparatory regimens			
FTBI/VP16/CY	10		
FTBI/VP16	11	52	
BU/VP16/CY	4		
FTBI/CY	2		20
CY	2		
BCNU/VP16/CY	1		

* Two patients with aplastic anemia and two patients with non-Hodgkin's lymphoma.

were good-risk and 6 poor-risk patients. The median age was 42 years with a range of 24 to 48.

GVHD prophylaxis. Patients who received matched sibling BMT received either cyclosporine/prednisone (CSP/PSE) (n = 13) or cyclosporine, methotrexate, and prednisone (CSP/MTX/PSE) (n = 17) as previously described for prophylaxis of GVHD.[16] In brief, patients received 5 mg/kg CSP intravenously (IV) from day −2 to +4, 3 mg/kg until day +15, 3.75 mg/kg until day +36, and then gradual tapering. Methylprednisolone was begun on day +7 at 0.5 mg/kg daily and increased to 1 mg/kg on day +15 until day +29 when patients were gradually tapered off steroids. Methotrexate (15 mg/m^2 IV) was given on days +1, and 10 mg/m^2 on days 3, and 6, respectively, when given with PSE, and also on day +11 (10 mg/m^2) for patients not receiving PSE. Patients with unrelated donors received CSP/MTX/PSE as prophylaxis for GVHD except for one patient who received CSP and anti-TAC (anti–interleukin-2 [IL-2] receptor) monoclonal antibody (MoAb) as part of a randomized study. All patients were graded for GVHD on a three-times-weekly basis by an experienced BM physician and a clinical nurse specialist using established criteria.[17]

Preparatory regimens. Preparatory regimes for allogeneic sibling and matched unrelated BMT for patients with good-risk disease consisted of fractionated total-body irradiation (FTBI) 1,320 cGy in 11 fractions on days −7 to −4, and either etoposide (VP-16) 60 mg/kg on day −3, or cyclophosphamide (CY) 60 mg/kg/d on days −3 and −2. Patients with advanced disease (AML or ALL greater than 1st CR, CML greater than 1st CP) received FTBI, VP-16 (60 mg/kg on day −4) and CY (60 mg/kg on day −2). Patients with myelodysplasia and secondary leukemia received busulfan (4 mg/kg/d) on days −7 and −6, VP-16 (45 mg/kg) on day −5 and CY (45 mg/kg/d) on days −3 and −2; those patients with aplastic anemia received CY (50 mg/kg/d) on days −5 to −2. BM was reinfused on day 0.

Supportive care. All patients received CMV$^-$, irradiated (2,500 cGy) blood products and oral gut decontamination with neomycin and vancomycin. G-CSF was started at 10 μg/kg/d on day +1 after marrow reinfusion in patients receiving cyclosporine/prednisone or day +6 for those also receiving methotrexate. G-CSF was administered over 1 to 2 hours via continuous intravenous infusion until the patients absolute neutrophil count (ANC) exceeded 1,000/μL for 3 consecutive days. On day +1 all patients were started on amphotericin 0.15 mg/kg daily and intravenous vancomycin (1 g every 12 hours) for fungal and bacterial prophylaxis.[18] Total parenteral nutrition and broad spectrum antibodies were used as clinically indicated. If fevers persisted despite adequate antibacteria coverage with negative blood cultures, amphotericin was increased to therapeutic doses (0.5 mg/kg/d).

The historical control group consisted of 52 patients treated at Stanford Medical Center who were part of a randomized controlled trial of GVHD prophylaxis.[15] All patients on the study group had low-risk disease as previously defined and received FTBI and etoposide as their preparatory regimen. The median age was 30 years (range, 16 to 40). Patient characteristics are shown in Table 1. Supportive care was identical between the groups.

Statistical analysis. The Mann-Whitney test was used to compare recovery of neutrophil and platelet counts. The chi-squared test was used to determine and compare the incidence of GVHD between groups.

RESULTS

Hematological recovery. Thirty patients received allogeneic matched sibling BM transplants. Seventeen (group 1) received CSP/MTX/PSE and 13 CSP/PSE as GVHD prophylaxis. One patient in the CSP/MTX/PSE group died before engraftment on day 23 and was not included in the engraftment data, but was included in the survival analysis. The median time for an ANC greater than 500/μL was 16 days (range, 14 to 27) in the CSP/MTX/PSE and 10 days (range, 8 to 13) in the CSP/PSE group (Table 2).

Patients treated with CSP/PSE engrafted significantly faster than those who received CSP/MTX/PSE as GVHD prophylaxis ($P < .001$). Time to ANC greater than 500/μL was significantly faster in patients who received G-CSF and GVHD prophylaxis with CSP/PSE compared with our historical control group (10 *v* 13 days; $P < .01$). We observed similar accelerated myeloid engraftment for those patients who received methotrexate for GVHD prophylaxis relative to our historical controls (16 *v* 19 days; $P < .05$).

The median day to platelet engraftment (platelet count greater than 20,000/μL independent of platelet transfusion) was 27 days (range, 17 to 119) for the MTX group and 23 days (range, 11 to 94) for the group not receiving MTX. The difference in the time to platelet engraftment between these two groups was statistically not significant. Compared with historical controls, there were no significant differences in platelet engraftment for the groups treated with or without MTX. The median number of red blood cell (RBC) transfusions was 12 (range, 7 to 92) and 16 units (7 to 43), respectively, for the groups who received MTX or no MTX as part of their GVHD prophylaxis. This was not different from the number of RBC transfusions required in the historical control group.

Twenty patients received matched unrelated donor BMT. The engraftment results are shown in Table 2. One patient died before engraftment on day +27 and was not included in the engraftment data, but was included in the survival analysis. The median time to an ANC greater than 500/μL was 17 days (range, 13 to 26). The median time to platelet

Table 2. Clinical Outcome

	Matched Sibling BMT With G-CSF		Matched Sibling BMT Controls		Unrelated Donor BMT With G-CSF
	CSA/MTX/PSE (n = 17)	CSA/PSE (n = 13)	CSA/MTX/PSE (n = 27)	CSA/PSE (n = 25)	CSA/MTX/PSE (n = 20)
Median days to ANC >500/μL (range)	16* (14-27)	10† (8-13)	19 (13-28)	13 (10-23)	17 (14-26)
Median days to platelets >20,000/μL (range)	27 (17-119)	23 (11-94)	23 (10-102)	22 (11-124)	41 (23-140)
Acute GVHD grade II-IV	8%	11%	9%	21%	21%
Relapse	8%	6%	13%	16%	15%
Day-100 DFS	84%	65%	64%‡	59%‡	40%

* $P < .001$ compared with patients CSA/PSE and $P < .005$ compared with historical controls treated with CSA/MTX/PSE.

† $P < .01$ compared with historical controls treated with CSA/PSE.

‡ Actuarial DFS.

engraftment greater than 20,000/μL was 41 days (range, 18 to 140). Patients were transfused with a median of 21 units of RBC during the course of their transplant.

Infectious complications. All 50 patients developed fevers while they were neutropenic and received broad spectrum antibiotic coverage empirically. If the patient did not defervesce promptly, amphotericin B was added at a dose of 0.5 to 1.0 mg/kg. Of the 30 patients undergoing sibling transplants, 14 developed documented infections during the period of neutropenia. One patient developed a fungemia before engraftment and died on day +33 despite granulocyte recovery. Two other patients died of complications related to septicemia after granulocyte recovery (Table 3). Of the 20 patients who underwent unrelated transplants, 14 patients developed documented infections. None of these patients died from bacterial infections, but of five patients who developed aspergillosis, the fungal infection was the contributing cause of death in three patients. Two of these patients developed *Aspergillus* infection before engraftment. However, all five patients who developed *Aspergillus* infection did so after being treated with high-dose steroids (2 mg/kg up to 1 g/d) for the treatment of diffuse alveolar hemorrhage or GVHD.

GVHD. Of the 17 matched sibling transplant recipients who received MTX as part of their GVHD prophylaxis, 2 patients (11%) developed acute GVHD (grade ≥ II). One patient had grade III disease and 1 with grade IV GVHD ultimately died of GVHD. In the 13 patients who did not receive MTX, 1 (8%) developed grade IV GVHD and subsequently died of GVHD. There were no differences in the incidence or severity of GVHD between patients treated with G-CSF and the historical controls (Table 2). Four of the 19 patients receiving matched unrelated transplants developed grade II-IV acute GVHD. Three of the 4 patients with grade II-IV subsequently died (1 of GVHD, 2 of fungal infections).

Table 3. Infectious Complications

Organism	Matched Related/ n (cause of death)	Matched Unrelated/ n (cause of death)
Gram-positive *cocci*	6 (0)	4 (0)
Gram-negative *cocci*	3 (2)	4 (0)
Cytomegalovirus	2 (0)	3 (1)
Aspergillus	1 (0)	5 (3)
Candida	1 (0)	1 (0)
Sceidosporium	1 (1)	0

Toxicity. All patients received full doses of G-CSF as planned, except the two who died before engraftment. None of the patients required discontinuation of G-CSF after allogeneic BM transplant secondary to GVHD or other complications before engraftment. When the G-CSF was discontinued, the white blood cell count fell in the majority of patients; however, no patient fell below an ANC of 500/μL or required reinstitution of treatment with G-CSF. There were no noticeable toxicities associated with the administration of G-CSF. Specifically there were no complaints of bony pain after administration of G-CSF.

Survival. Six of the 30 patients who received allogeneic matched sibling BM transplants died in the first 100 days, 2 of sepsis, 2 of GVHD and 1 each of venocclusive disease (VOD) and fungemia. Two patients have relapsed on days 62 and 78 posttransplantation. Twenty two patients are alive and well with median follow-up of 190 days. Nine of the 20 patients who received matched unrelated BM transplants died in the first 100 days (5 of fungemia, 3 of VOD, and 1 with VOD/GVHD). Three patients (AML with induction failure, ALL 4th CR, secondary AML) have relapsed on days 27, 58, and 64 posttransplantation.

DISCUSSION

Allogeneic BMT is increasingly being used as a treatment for hematologic malignancies. Colony-stimulating growth factors have been used in attempts to speed myeloid recovery and reduce the length of this high-risk period.

There are currently only two studies using G-CSF after allogeneic matched sibling donor BMT.[14,15] In the first multicenter trial, G-CSF was begun on day 3 or 5 after reinfusion of donor marrow. Doses ranged from 200 to 800 $\mu g/m^2$ given IV over 30 minutes. Thirty-four patients were evaluated. Time to an ANC greater than 500/μL was 14 to 15 days. There were no differences attributable to increasing G-CSF doses. Although details of the comparison group were not given in the trial, engraftment was significantly

faster compared with patients treated previously without growth factors. There were no toxicities attributable to G-CSF, specifically no increases in relapse or GVHD were noted. The second trial treated 19 patients with G-CSF or placebo in doses ranging from 2 to 20 μg/kg/d as part of a large study investigating the use of G-CSF after BMT. They did not see an increase in GVHD in patients who received G-CSF. There were more deaths in the G-CSF–treated group versus the group receiving placebo, but patient numbers are very small (5 controls, 14 patients receiving G-CSF).

Our trial was performed at a single institution and showed that patients treated with G-CSF who received HLA matched sibling BMT had a significantly faster myeloid engraftment compared with a similarly treated historical control group. As has been shown with GM-CSF, the effect of G-CSF was less pronounced in those who received MTX as a component of their GVHD prophylaxis.[13] There was no effect on either platelet or RBC engraftment in the G-CSF–treated group compared with historical control patients.

Our historical control group consisted of 52 patients treated at our institution who received identical supportive care to the G-CSF treated group. This group was composed entirely of good-risk disease patients. Theoretically, our control group who had received less chemotherapy before transplantation would have less potential damage to the underlying stromal cells and might have been expected to engraft faster than the more heavily pretreated G-CSF group. Despite this, the G-CSF group engrafted significantly faster than the historical control group, suggesting that G-CSF is capable of accelerating myeloid engraftment. Moreover, we would also have expected that this group of patients with a 40% (12 of 30) incidence of poor-risk disease would have a greater incidence of GVHD and relapse than the historical control group.[19,20] We did not observe a difference in the incidence of acute GVHD and 100-day survival between the G-CSF–treated group and our historical control group. Although longer follow-up is necessary, there was no apparent increase in the relapse rate in patients treated with G-CSF.

Recent studies have investigated the role of growth factors after matched unrelated BMT. Although a decrease in febrile days and septicemic episodes was noted,[12] a phase II trial using GM-CSF showed no difference in time to an ANC greater than 500/μL in the GM-CSF–treated group relative to controls. Importantly, no increase in incidence or severity of GVHD was noted in the GM-CSF–treated group. The results of a phase III trial using GM-CSF after matched unrelated BMT have recently been presented.[13] There was accelerated myeloid engraftment seen in the group treated with GM-CSF without a difference in bacteremia. Although there was a trend towards decreased survival in the group treated with GM-CSF, no difference in GVHD, relapse, or disease-free survival (DFS) was observed between the GM-CSF group compared with placebo group. There have been no previous reports using G-CSF after matched unrelated BMT. In our series, 20 patients were treated. All patients received MTX as a component of their GVHD prophylasxis. The time to an ANC greater than 500/μL of 17 days compared favorably with patients treated without growth factors.[19,21]

The incidence of grade II-IV acute GVHD after matched unrelated BMT was surprisingly low at 20% in our patients treated with G-CSF. This low incidence of GVHD may in part be caused by the fact that four patients died before day 30 (three VOD, one fungemia) without evidence of GVHD. As a consequence, despite the low incidence of GVHD, our 100-day DFS of 40% is similar to results reported in the literature.[21,22] Of concern is that 9 patients (45%) died within 100 days of the date of the BMT. In the recent randomized controlled trial comparing GM-CSF with placebo after matched unrelated BMT,[13] a similar trend to increased early death (26% *v* 13%) was seen in the group treated with growth factors compared with patients receiving placebo. Although it seems unlikely that G-CSF contributed to the cause of death in these patients, it is important that these results be verified in the setting of a randomized trial.

Our study suggests that G-CSF may accelerate myeloid engraftment in allogeneic matched sibling and matched unrelated BMT. There does not appear to be an increase in the incidence of acute grade II-IV GVHD or relapse in allogeneic matched sibling BMT patients treated with G-CSF. Our trial was not a randomized placebo controlled trial. Only through such trials will one be able to unequivocably show whether G-CSF is capable of acclerating engraftment after allogeneic BMT without an increase in toxicity. These trials are particularly important in the study of matched unrelated BMT given the apparent increase in early toxicity seen in our study.

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