Long-Term Follow-up of a Phase III Study of Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor After Autologous Bone Marrow Transplantation for Lymphoid Malignancies

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One hundred and twenty-eight patients with non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD), and acute lymphoblastic leukemia (ALL) previously reported from a phase III trial of rhGM-CSF or placebo following autologous bone marrow transplantation (ABMT) were investigated for the development of late toxicities. Median follow-up is 36 months. No apparent long-term deleterious effects on BM function were observed. Moreover, disease-free survival and overall survival were similar for patients on both treatment arms, arguing for the long-term safety of recombinant human granulocyte macrophage-colony-stimulating factor (rhGM-CSF). The only factors predictive for both a high risk of relapse over time and mortality were having the diagnosis of ALL and/or undergoing ABMT in resistant relapse. We attempted to identify clinical variables before BM harvest, at the time of marrow infusion, or events within the first 100 days posttransplant, which might predict speed of neutrophil recovery in the setting of placebo or rhGM-CSF administration after ABMT. Only previous exposure to agents that deplete stem cells led to a significant delay in neutrophil recovery, suggesting their avoidance in patients who may undergo ABMT. Nevertheless, even those patients benefited from rhGM-CSF. For all patients, rhGM-CSF and agents that deplete stem cells were the strongest independent predictors for neutrophil engraftment. With the increasing use of newer hematopoietic growth factors both alone and in combination, long-term follow-up is essential to confirm the same safety that we report with rhGM-CSF.

THE TREATMENT of lymphoma, leukemia, breast cancer, and other chemotherapy sensitive solid tumors with various high-dose ablative regimens followed by autologous bone marrow transplantation (ABMT) has dramatically increased in frequency over the past 5 years.[1] This strategy is based on the premise that intensification of cytotoxic dose may be an important determinant in achieving cure for these malignancies. To date, lymphoma is the most common malignancy for which ABMT is performed, with 40% to 50% 5-year disease-free survivals reported in multiply relapsed patients with sensitive disease.[2-5] However, transplant related mortality continues to range from 5% to 30%, primarily as a result of infection and/or bleeding complications due to the prolonged aplasia following marrow infusion.[6] These complications may occur despite the use of supportive measures, which include patient isolation, antibiotic administration, and vigorous blood product support.

Since the above complications increase with the length of aplasia, myeloid stimulating growth factors such as recombinant human granulocyte macrophage-colony-stimulating factor (rhGM-CSF) and rhG-CSF have been used in the hope of hastening engraftment and decreasing the morbidity and mortality associated with both standard chemotherapy and high-dose ablative regimens. Studies have supported the use of these factors in both the ABMT and peripheral blood stem cell transplant setting as well as more widespread clinical practice.[7-16] Although widely used, questions and concerns remain regarding the risk of late toxicity from growth factor administration, including graft failure, leukemogenesis, and increased relapse rates.

In June 1991, we first reported the results of a phase III randomized trial in which rhGM-CSF or placebo was administered following ABMT to 128 patients with relapsed non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD), and acute lymphoblastic leukemia (ALL).[7] The last patient was entered on the study on March 30, 1990. The median follow-up was 36 months. Our results indicated that those patients receiving rhGM-CSF experienced significantly hastened neutrophil recovery, shorter hospitalization, and fewer days on antibiotics. No significant differences in acute toxicities were identified between the patients who had received rhGM-CSF and those who had received placebo. Considering that this was a large randomized study with a relatively long median follow-up, we performed a subsequent analysis to answer the questions regarding the long-term impact of rhGM-CSF on graft failure, leukemogenesis, disease-free survival, and overall survival.

Long-term follow-up demonstrates that no long-term deleterious effects on marrow function, relapse, or survival were seen, arguing for the long-term safety and efficacy of rhGM-CSF in patients with lymphoid malignancies undergoing ABMT. In addition, an attempt was made to identify those clinical variables before BM harvest, at the time of marrow infusion, or events within the first 100 days posttransplant, which might predict for neutrophil engraftment as well as responsiveness to growth factor administration. The results confirm the beneficial effects of rhGM-CSF.

MATERIALS AND METHODS

Selection of patients and treatment protocol. A total of 128 patients (ages 3 to 62) underwent ABMT for relapsed NHL, HD, ALL,

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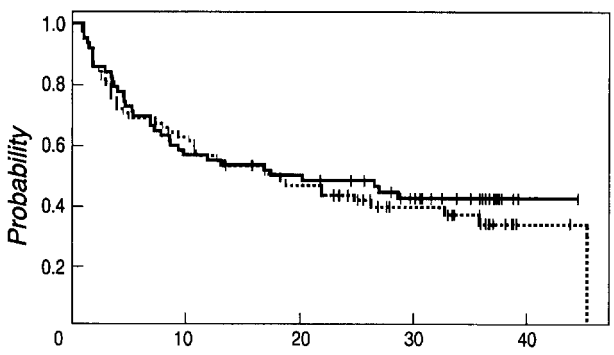
or acute myelogenous leukemia (1 patient) at Dana-Farber Cancer Institute (DFCI) in Boston, University of Nebraska Medical Center (UNMC) in Omaha, and Fred Hutchinson Cancer Research Center (FHCRC) in Seattle between May 1988 and March 1990. Sixty-three patients were randomized to receive placebo and 65 patients were randomized to receive yeast derived rhGM-CSF at a dose of 250 $\mu g/m^2$ as a 2-hour infusion for a 21-day period following marrow infusion. As has been previously reported,[7] comparable numbers of patients within each disease category were randomized to each treatment arm. Informed consent, conforming to the guidelines of the Food and Drug Administration and those of institutional review boards, was required at all centers.

Definition of neutrophil engraftment. Engraftment was defined as the first of 2 consecutive days with an absolute neutrophil count (ANC) of $\geq 500/\mu L$. Day 1 was defined as the day of BM infusion. Seven of the 128 patient cohort were censored due to death before engraftment and an additional four were censored due to a lack of 2 consecutive day documentation regarding the achievement of an ANC of $\geq 500/\mu L$. Time to an ANC of $\geq 100/\mu L$ was also examined, with a total of three patients censored from analysis due to early death or lack of 2 consecutive day documentation. Late graft failure was defined as the loss of engraftment, with a mean ANC of $<500/\mu L$ for at least 1 week after having initially achieved a mean ANC $\geq 500/\mu L$ for 1 week. Patients with leukemic relapse or potentially reversible pharmacologic causes of graft failure from trimethoprim-sulfamethoxazole, acyclovir, or vancomycin were excluded.

Clinical outcome. Information was available regarding neutrophil engraftment as well as the incidence of late toxicities, graft failure, disease-free survival, and overall survival for all patients entered on the study, with a median follow-up of 36 months.

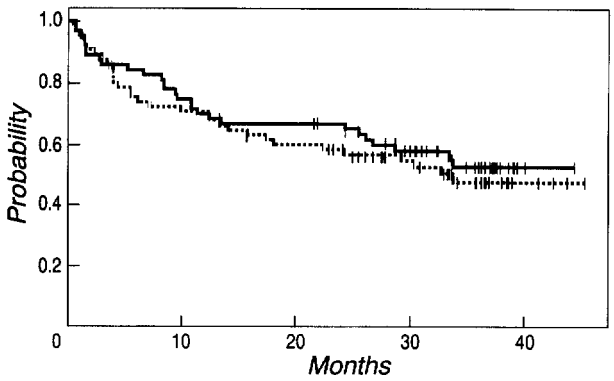
Clinical variables. A retrospective analysis of several patient characteristics was performed to assess their value as predictors of neutrophil recovery following BM infusion. These characteristics were categorized into three groups: pre-harvest variables, variables present at the time of marrow infusion, and events within the first 100 days posttransplant. Relapses were classified as sensitive if patients achieved a complete remission or partial remission with chemotherapy and/



Group	Time Interval 0-10	10-20	20-30	30-40	40-50
— Placebo	27/63	5/36	3/30	0/20	0/1
····· rhGM-CSF	24/65	10/41	4/30	2/17	1/2

(# events / # at risk)

Fig 1. Kaplan and Meier curves for DFS in the 128 patients with lymphoid malignancies according to randomization to either placebo or rhGM-CSF following ABMT. (—) Patients alive in continuous CR on the placebo arm. (· · ·) Patients alive in continuous CR on the rhGM-CSF arm. There is no difference in DFS for the two groups ($P = .58$).



Group	Time Interval 0-10	10-20	20-30	30-40	40-50
— Placebo	16/63	5/47	5/41	2/28	0/2
····· rhGM-CSF	19/65	7/46	3/38	3/26	0/4

(# events / # at risk)

Fig 2. Kaplan and Meier curves for OS in the 128 patients with lymphoid malignancies according to randomization to either placebo or rhGM-CSF following ABMT. (—) Patients alive on the placebo arm. (· · ·) Patients alive on the rhGM-CSF arm. There is no difference in OS for the two groups ($P = .55$).

or radiotherapy before admission for ABMT. Partial remission was defined as a shrinkage of at least 50% in the largest dimension of all measurable tumor sites. Resistant relapse was defined as failure to achieve a partial remission or disease progression with chemotherapy and/or radiotherapy before admission for ABMT. Patients in untreated relapse had not received chemotherapy and/or radiotherapy before admission for ABMT. Of the 17 patients with ALL, 6 were in complete remission, 7 were in untreated relapse, and 4 were in resistant relapse at the time of ABMT. Only two patients had previously received pelvic irradiation, at doses of 3060 cGy and 5040 cGy, respectively. Several chemotherapy drugs were defined as agents that deplete stem cells because of evidence in mice and/or humans for damage to primitive stem cells and later progenitors.[17-24] For this analysis, agents that deplete stem cells included: busulfan, BCNU, CCNU, chlorambucil, procarbazine, and nitrogen mustard. To assess the degree of chemotherapy exposure before BM harvest we divided patients into two categories: those who received at least the median (7) total number of chemotherapy drugs and those who received less than the median total number of drugs.

Statistical methods. Time to engraftment was compared using the Wilcoxon test; disease-free survival and overall survival were compared using the log-rank test. Plots of engraftment, disease-free survival, and overall survival use the method of Kaplan and Meier. Median times to events were also calculated using this method. Stepwise Cox proportional hazards regression was used to build models for DFS and OS. Associations between categorical variables were assessed by the Fisher exact test.

RESULTS

ABMT patients treated with rhGM-CSF experience no long-term toxicities. With a median follow-up of 36 months for the 128 patients with lymphoid malignancies who underwent ABMT, there was no evidence that patients who received rhGM-CSF *v* placebo experienced an increased risk of graft failure, leukemogenesis, relapse, or death. In fact, no patient in either group developed late graft failure. Figures 1 and 2

Table 1. Potential Predictive Variables for Relapse and Survival

	No. of Patients	No. of Relapses (%)	No. of Deaths (%)
No. of chemotherapy drugs received before ABMT			
<7	56	26 (46)	24 (43)
≥7	72	38 (53)	36 (50)
Previous radiation therapy before ABMT			
–	71	30 (42)	25 (35)
+	57	34 (60)	35 (61)
Disease type at ABMT			
NHL	87	35 (40)	36 (41)
Hodgkin's	23	16 (70)	8 (35)
Leukemia	18	13 (72)	16 (89)
Relapse status at ABMT			
Sensitive	81	30 (37)	27 (33)
Resistant	36	25 (70)	24 (67)
Untreated	11	9 (82)	9 (82)
Preparative regimen at ABMT			
TBI containing	97	45 (46)	47 (48)
Chemotherapy alone	31	19 (61)	13 (42)
BM infusion			
Purged	71	32 (45)	29 (41)
Unpurged	57	32 (56)	31 (54)
rhGM-CSF or placebo after BM infusion			
rhGM-CSF	65	35 (54)	32 (49)
Placebo	63	29 (46)	28 (44)

show essentially overlapping Kaplan Meier curves of disease-free survival and overall survival for patients on both treatment arms. Therefore, exposure to rhGM-CSF had no significant effect on disease-free survival (P = .58) or overall survival (P = .55). Investigations of the time to relapse as well as time to death similarly showed no difference between patients who received rhGM-CSF *v* placebo.

We examined a series of variables that might affect disease-free or overall survival. Table 1 presents the number of relapses and number of deaths within the categories of these variables. We used the Cox proportional hazards model to distinguish those variables that were predictive for disease-free survival and overall survival. Only two variables were found to have a significant impact. Those patients with the diagnosis of lymphoid leukemia were at significantly increased risk for relapse over time as well as for death in comparison to the patients with HD and NHL. In addition, those patients in resistant relapse at the time of admission for ABMT had significantly decreased disease-free survival and overall survival. When treatment with rhGM-CSF or placebo was added to the model, no effect on either relapse or survival was observed. Those patients with a diagnosis of HD and those in an untreated relapse at the time of admission for ABMT did not experience a significantly increased risk of relapse or death. Other factors that did not significantly impact disease-free or overall survival were number of chemotherapy drugs received, prior radiation therapy, and the use of monoclonal antibody (MoAb)-purged bone marrow.

Analysis of clinical variables likely to predict for the speed of neutrophil engraftment following ABMT. A number of variables were examined before BM harvest in an attempt to identify those that might predict for neutrophil recovery. Table 2 presents the median number of days to achievement of an ANC of ≥100/μL and ≥500/μL for these variables. For the 128 patients examined, the median number of days to an ANC of ≥100/μL was 14 and ≥500/μL was 22. A total of 87 patients had NHL, 23 patients had HD, and 18 patients had leukemia. Those patients with the diagnosis of HD appeared to exhibit delayed neutrophil recovery to both an ANC ≥100/μL and ≥500/μL (P = .07) in comparison to patients with NHL or leukemia. A strong association was identified between having the diagnosis of HD and prior receipt of stem cell depleting agents. A total of 21 (91%) of 23 patients with HD had received such agents preharvest, while only 22 (21%) of the remaining 105 patients had been exposed to agents that deplete stem cells. The Fisher's exact test for association is <.0001. Therefore, previous exposure to stem cell depleting agents may account for the delay in neutrophil recovery observed for those patients with HD. In fact, prior receipt of such agents was found to be associated with a delay in recovery to an ANC of ≥500/μL (P = .0008). Additional preharvest variables, including the total number of chemotherapy drugs received as well as previous radiation therapy, appeared to have no impact on neutrophil engraftment. In addition, there was no association between the variables of age and sex with neutrophil recovery (not shown).

We examined several variables present at the time of BM infusion for their relationship with neutrophil recovery. All patients with HD received chemotherapy without irradiation followed by unpurged marrow infusion. As shown in Table

Table 2. The Relationship of Preharvest Variables and Variables at the Time of BM Infusion to Neutrophil Recovery Following ABMT

	No. of Patients	Median Day to ANC ≥100/μL	Median Day to ANC ≥500/μL
Total no. of patients	128	14	22
Disease type			
NHL	87	14	21
Hodgkin's	23	20	29
Leukemia	18	14	22
Prior exposure to agents that deplete stem cells*			
–	85	14	19
+	43	17	28
Prior no. of drugs			
<7	56	13	21
≥7	72	15	22
Prior radiation therapy			
–	71	14	21
+	57	14	23
Bone marrow			
Purged	71	14	22
Unpurged	57	15	22
Relapse status			
Sensitive	81	14	22
Resistant	36	14	20
Untreated	11	14	22

* Agents that deplete stem cells included busulfan, BCNU, CCNU, chlorambucil, procarbazine, and nitrogen mustard.

2, there was no association identified between the type of BM infused (purged *v* unpurged) or relapse status and engraftment. The lack of an influence for BM purging on the rate of engraftment likely reflects the differential effect on depletion of marrow progenitors by purging with MoAbs and complement (as was done in this study) *v* chemotherapy agents such as 4-hydroperoxycyclophosphamide (4-HC). Finally, the number of days between BM harvest and infusion had no impact on neutrophil recovery (not shown).

We were interested in examining the influence of events that occurred during the first 100 days posttransplant on neutrophil engraftment. A large number of patients on this study received antibiotics for fever, with comparable numbers treated from both the rhGM-CSF and placebo arms. However, as previously reported, there was a significantly shorter duration of intravenous antibiotic administration for those patients who had received rhGM-CSF.[7] We could not detect an impact of these agents on neutrophil recovery. Since other complications occurred with low frequency, it was impossible to assess whether they impacted on recovery.

The independent predictive effect of rhGM-CSF on neutrophil recovery. We were interested in assessing whether treatment with growth factor exerted an independent beneficial effect on neutrophil recovery across all clinical variables. As shown in Table 3, rhGM-CSF appeared to hasten neutrophil recovery following marrow infusion irregardless of disease type, previous exposure to agents that deplete stem cells, prior number of drugs, radiotherapy exposure, marrow purging, type of preparative regimen, or relapse status at ABMT. The original study had not been designed for subsequent subset to have power to detect analysis, and consequently the sample sizes were too small to detect significant differences within categories of a variable. Therefore, although it appeared that patients in all categories experienced a more rapid median time to an ANC of $\geq 500/\mu L$, small sample sizes make it inappropriate to carry out formal statistical assessment within each subset. However, the descriptive consistency of the data is evident. In conclusion, both the administration of rhGM-CSF and prior exposure to agents that deplete stem cells were the strongest independent predictors for the speed of neutrophil recovery following ABMT for lymphoid malignancies.

Table 3. Influence of rhGM-CSF on Neutrophil Recovery With Respect to Clinical Variables

	Median Day to ANC $\geq 500/\mu L$		*P*
	rhGM-CSF	Placebo	Value*
Total no. of patients	19	25	.0028
Disease			.0011
NHL	18	24	
Hodkgin's	24	30	
Leukemia	18.5	23	
Stem cell poisons			.0028
−	18	23	
+	25	29	
Prior no. of drugs			.0035
<7	18	23	
≥7	19	28	
Prior radiation therapy			.0024
−	18	25	
+	19.5	26	
Bone marrow			.0028
Unpurged	18	28	
Purged	19	24	
Preparative regimen			.0023
TBI containing	18	24	
Chemotherapy alone	23	29.5	
Relapse status at ABMT			.0031
Sensitive	19	27	
Resistant	20	20	
Untreated	19	22.5	

* *P* value for effect of rhGM-CSF using a stratified Wilcoxon test.

DISCUSSION

One year ago, both rhGM-CSF and rhG-CSF were approved for clinical use in the setting of neutropenia following ABMT or chemotherapy for various malignancies. However, concerns have remained regarding the potential for long-term harmful effects, either in the form of unexpected toxicities or increased relapse and/or mortality rates. The present report should allay some of these concerns. We have demonstrated that rhGM-CSF was not associated with long-term toxicities in the form of either graft failure, leukemogenesis, increased relapse rates, or increased mortality in a large cohort of patients who received the agent as part of a phase III randomized study following ABMT for lymphoid malignancies. The only factors identified as predictive for a high risk of relapse over time and death were having the diagnosis of lymphoid leukemia and/or undergoing BMT while in resistant relapse.

In addition, we examined in detail all characteristics that might predict for the speed of neutrophil recovery in the setting of either placebo or rhGM-CSF administration after ABMT. These variables were categorized as pretransplant characteristics, characteristics at the time of BM infusion, and events within the first 100 days posttransplant. Both univariate and multivariate analysis failed to identify characteristics predictive of the speed of neutrophil recovery post-ABMT. Only prior exposure to agents that deplete stem cells led to a significant delay in neutrophil recovery; but even those patients appeared to benefit from the administration of rhGM-CSF.

Other studies evaluating the efficacy of rhGM-CSF in the setting of chemotherapy and/or allogeneic BMT for patients with acute myeloblastic leukemia (AML), chronic myelogenous leukemia (CML), myelodysplasia (MDS), or multiple myeloma (MM) suggest that it does not stimulate tumor cell growth, although follow-up is relatively short as compared with this trial.[25-30] These findings are in contrast to the results often seen in vitro when the malignant cells are exposed to rhGM-CSF. In the presence of interleukin-6, rhGM-CSF has been reported to be a potential myeloma growth factor in vitro.[31] Nevertheless, Barlogie et al[28] administered rhGM-CSF subcutaneously to 23 patients with refractory myeloma following therapy with high-dose melphalan. In addition to its beneficial effect, rhGM-CSF appeared to have no obvious stimulatory effects on myeloma cell growth. No increases in either marrow plasmacytosis or myeloma protein concentrations were identified on weekly monitoring. Moreover, re-

lapse-free and overall survival in that study were comparable between these patients and historical controls. Other investigators have administered rhGM-CSF as well as rhG-CSF in the setting of allogeneic BMT for MM, AML, MDS, and CML.[27,29,32] However, only two groups addressed the question of the potential impact on relapse rates. Masaoka et al[27] reported that in patients with AML and CML who received rhG-CSF following allogeneic BMT, relapse rates at both 6 and 12 months were similar to those of historical patients. Similarly, Powles et al[32] administered rhGM-CSF *v* placebo in a double-blind controlled trial following allogeneic BMT for patients with AML and CML. Despite their observation that leukemic cells could be stimulated to produce colonies in vitro, there was no significant difference in survival between the two groups. In addition, none of the 13 patients with myeloid leukemia who received rhGM-CSF relapsed at a median of 1 year of follow-up. Several investigators[25,26,30] have described increases in circulating blasts during rhGM-CSF administration in patients with MDS. However, the number of blasts usually, but not always, decreased following the discontinuation of treatment.

To date, few studies using myeloid CSFs in the setting of BMT have addressed the question of whether specific clinical variables can predict for the speed of neutrophil recovery. This question was most recently addressed by Advani et al[33] in the setting of a phase III trial of rhGM-CSF following autologous and/or peripheral stem cell transplantation for 69 patients with relapsed HD and NHL. However, interpretation of the data was made difficult due to the relationship between the variables analyzed. Prior exposure to agents that deplete stem cells was not evaluated in their model. Using multivariate analysis, the investigators identified the use of unpurged BM, infusion of peripheral blood stem cells, and administration of rhGM-CSF to be the factors of greatest impact on hastening neutrophil recovery. Normal hematopoietic recovery following BMT requires both early engraftment with recovery of peripheral blood cells as well as long-term stability of hematopoiesis. Differing subpopulations of marrow stem cells and progenitor cells mediate this recovery.[34,35] Several investigators have shown that various cytotoxic drugs can be divided into groups according to their ability to deplete BM stem cells.[17-24,34,36] Busulfan, BCNU, CCNU, chlorambucil, and the mustards appear to be more potent in this regard. The agents cytosine arabinoside, 5-fluorouracil, and hydroxyurea appear to have a minimal effect on primitive stem cells.[19,37,38] Many patients undergoing ABMT have been previously exposed to cytotoxic drugs that may act as agents that deplete stem cells and thereby lead to impaired hematopoietic recovery. Using an in vivo murine model, Neben et al[39] examined the effects of exposure to a variety of chemotherapy drugs on the ability of syngeneic BM to provide long-term hematopoiesis in lethally irradiated mice. Animals transplanted with marrow that had been previously treated with busulfan or BCNU exhibited a long-term decrease in peripheral blood counts, bone marrow cellularity, CFU content, and marrow self renewal. In contrast, hematopoietic recovery was better in those animals that received cyclophosphamide or cisplatin and normal for those that had received marrow exposed to cytosine arabinoside. These results suggest, as shown from our analysis, the importance of avoiding treatment with agents that deplete stem cells in patients for whom ABMT may be a consideration, because of their negative effects on both short-term hematopoietic recovery as well as potentially the long-term stability of the graft.

In the future, perhaps all patients and, in particular, those with low numbers of progenitors will benefit from the addition of peripheral blood stem cells to autologous marrow and/or priming of harvested marrow with growth factors alone or in combination. The beneficial effects of rhGM-CSF may be synergistic with rhG-CSF, interleukin-3, interleukin-1, and c-kit ligand[40,41] to induce more rapid neutrophil, as well as potentially platelet or erythroid recovery. The safest and most efficacious way to administer these factors in various combinations remains to be established in the setting of clinical trials. Throughout this exciting process, we will need to continue to monitor patients for both short- and long-term toxicities. We are hopeful that the long-term follow-up of patients entered on clinical trials using these newer CSFs and combinations of hematopoietic growth factors will reveal the same safety that we have reported with rhGM-CSF.

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