Long-Term Follow-up of Patients With Invasive Fungal Disease Who Received Adjunctive Therapy With Recombinant Human Macrophage Colony-Stimulating Factor

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Mortality of bone marrow transplant (BMT) patients who develop invasive fungal infection is greater than 80%. Long-term follow-up of 46 consecutive BMT patients who received recombinant human macrophage colony-stimulating factor (rhM-CSF) as adjunctive therapy with standard antifungal treatment who were entered into phase I/II trials at The Fred Hutchinson Cancer Research Center is reported. rhM-CSF (100 μg/m² to 2,000 μg/m²; Chiron/Cetus Corporation, Emeryville, CA) was administered from day 0 to 28 after determination of progressive fungal disease. Results of long-term follow-up of fungal infection, relapse, and survival were compared with 58 similar historical controls. Multivariable analysis of the patients who received rhM-CSF showed two factors that significantly correlated with poor survival: Karnofsky score ≤ 20% and *Aspergillus* infection. Overall, survival of patients who received rhM-CSF was greater than that of historical patients (27% *v* 5%) and was entirely because of a 50% survival rate in patients with *Candida* infection and Karnofsky scores greater than 20%. Prospective, randomized, controlled trials to determine efficiency of rhM-CSF are indicated and should be directed at patients with invasive candidiasis.

TEN PERCENT of patients undergoing allogeneic bone marrow transplantation (BMT) will develop invasive fungal disease with an associated high morbidity and mortality.[1-3] Prophylactic treatment with antifungal agents or use of laminar air flow rooms may reduce the incidence of fungal infection[4,5]; however, once infection develops, little therapy other than treatment with amphotericin is available.

Recombinant human macrophage colony-stimulating factor (rhM-CSF) is a cytokine that stimulates the survival, proliferation, and differentiation and enhances the function of monocytes and macrophages.[6,7] Preclinical studies show that this activity is associated with a substantial increase in the ability of monocytes and macrophages to kill fungi.[8] rhM-CSF was well tolerated when administered to patients who developed invasive fungal infection after BMT[9] and in patients with metastatic cancer.[10] Other than thrombocytopenia, which was a dose-limiting toxicity, no other significant side effects were observed. Several patients had resolution of fungal infection contemporaneously with rhM-CSF and amphotericin treatment[9]; however, long-term assessments were not performed. This article reports long-term follow-up of the 24 rhM-CSF–treated patients who were originally reported in addition to 22 consecutive patients who received rhM-CSF at the maximum tolerated dose of 2,000 μg/m²/d.

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MATERIALS AND METHODS

Patient selection. Patients with presumed or documented fungal infections before or after BMT were eligible. No exclusions were made for diagnosis, age, graft-versus-host disease (GVHD) status or Karnofsky performance scores. Results of the first 24 patients have been previously published.[9] Subsequently, an additional 22 consecutive patients who received rhM-CSF at 2,000 μg/m²/d were entered into trial. Clinical characteristics of the 46 patients who received rhM-CSF are shown in Table 1. Informed consent conforming to Federal Drug Administration and Institutional Review Board Guidelines was required. Comparison of study patients was made to historical control patients. A summary of the characteristics of both patient groups is shown in Table 2.

Patient eligibility. Patients were included if they had one of the following characteristics: documented invasive fungal infection demonstrated by histologic analysis or cultures of closed-body fluids or tissue biopsies, a single, positive blood culture with radiologic evidence of invasive disease, two or more positive blood cultures for *Candida* species without a documented local site of infection, or persistent fever with fungi dated from bronchial alveolar lavage fluid with radiologic studies suggestive of fungal infection.

Clinical monitoring. All patients were examined daily while receiving rhM-CSF. Bone marrow aspirates and biopsies were performed before therapy to rule out malignancy. Blood cultures were taken as clinically indicated. Chemistries and complete blood cell counts were performed daily. Evaluation of fungal infection was performed by repeating the initial diagnostic procedure when possible or at autopsy. Long-term follow-up, evaluation for the persistence of fungal infection, cause of death, and survival was made by review of medical records and phone conversations with the patient's primary physician. Diagnostic procedures originally used to document fungal infection were repeated when possible or at autopsy.

Study design. The design of the study into which the initial 24 patients were entered has been previously described.[9] The subsequent 22 patients received rhM-CSF at a dose of 2,000 μg/m²/d by 2-hour intravenous infusion for 28 consecutive days. rhM-CSF (specific activity: 1×10^8 U/mg; Cetus Corporation, Emeryville, CA) was administered in 100 mL of normal saline with 0.25% albumin by central venous catheter. All patients received amphotericin at maximally tolerated doses (.5 to 1.0 μg/kg/d). Results were compared with 58 historical patients who were retrospectively identified

Table 1. Characteristics of 46 Patients With Invasive Fungal Infection Who Received rhM-CSF

UPN	Age/Sex (M/F)	Received Pentoxifyllene (Y/N)	Maximum Dose M-CSF $\mu g/m^2$	Diagnosis/ State	TBI/LAF (Y/N)	BMT Type	Pre–M-CSF Karnofsky	GVHD/Grade Pre–M-CSF	Organ Involved	Day M-CSF Started After BMT	Day F/U S/P M-CSF*	COD	Evaluation of Fungus Day F/U*	Fungus Type
5514	23/F	Y	2,000	ALL/rel	Y/N	URD	50	N/A	Lung	Pre	361	Relapse	–	*Aspergillus*
5143	40/F	N	1,000	NHL/rel	N/N	Sib-M	40	III	Liver	113	193	GVHD	–	*C albicans*
5402	20/F	N	1,000	AML/rel	Y/Y	URD	40	III	Blood	27	54	GVHD	–	*C albicans*
5049	22/F	Y	500	AML/rel	Y/N	Sib-M	20	II	Blood	108	9	Pneumonitis	–	*C parapsilosis*
5392	42/M	N	1,000	ALL/rel	N/N	Auto	20	N/A	CSF	26	12	CV Failure	–	*C tropicalis*
5452	39/F	N	1,000	NHL/rem	N/Y	Auto	50	N/A	Skin	18	779+	N/A	–	*Candida*
5552	22/F	Y	2,000	AML/rem	Y/Y	Sib-M	50	N/A	Liver	Pre	776+	N/A	–	*Candida*
5238	11/F	N	2,000	AA	N/Y	Sib-M	50	I	Liver	184	659+	N/A	–	*Candida*
5415	44/M	N	1,500	AML/rel	Y/Y	Auto	20	N/A	Blood	14	8	Fungus	+	*Candida*
5435	25/M	N	2,000	AA	N/Y	Sib-M	40	N/A	Liver	Pre	770+	N/A	–	*Candida*
5237	8/M	N	2,000	ALL/rel	Y/N	URD	30	III	Lung	201	127	GVHD	+	*Aspergillus*
5497	52/F	Y	2,000	AML/rel	Y/Y	URD	20	I	Lung	47	20	MOF	–	*Aspergillus*
4647	50/M	Y	2,000	MDS	Y/Y	URD ×2	30	III	Skin	133	32	CMV	+	*Aspergillus*
5240	41/M	N	2,000	CML-AP	Y/Y	URD	20	II	Brain	117	2	Fungus	+	*Aspergillus*
1186	43/M	Y	2,000	AML/rel	Y/Y	Sib-M ×2	30	0	Blood	23	10	Resp Fail	UNK	*Candida*
5598	33/F	Y	2,000	AML/rel	Y/Y	Sib-M	50	N/A	Liver	Pre	83	CMV	–	*Candida*
5564	14/M	N	2,000	AML/rem	Y/N	Sib-M	50	0	Blood	25	716+	N/A	–	*Candida*
5226	3/F	N	2,000	AA	N/N	N/A	40	N/A	Skin	Pre	43	Resp Fail	–	*Aspergillus*
5640	14/F	N	2,000	ALL/rel	Y/N	Sib-M	50	N/A	Liver	Pre	193	Relapse	–	*Candida*
4697	51/M	N	2,000	NHL/rel	Y/N	Auto	20	N/A	Blood	30	12	Fungus	+	*C albicans*
5622	33/F	Y	2,000	NHL/rel	N/N	HLA-lag	30	I	Lung	42	16	Fungus	+	*Aspergillus*
4945	7/F	N	100	ALL/rel	Y/N	HLA-2ag	30	III	Liver	13	25	GVHD	–	*Candida*
4991	46/M	N	200	NHL/rel	N/N	Auto	30	N/A	Blood	13	903+	N/A	–	*C albicans*
5195	24/F	N	100	AA	N/N	Sib-M	20	0	Lung	66	70	Pneumonia	+	*C Parapsilosis*
5269	44/F	N	100	ALL/rel	Y/N	Sib-M	20	III	Blood	25	10	Resp Fail	+	*C Parapsilosis*
5718	27/F	N	1,000	CML/CP	Y/N	Sib-M ×2	40	N/A	Blood	11	625+	N/A	–	*C Tropicans*
5549	37/F	Y	2,000	CML/CP	Y/N	URD	30	I	Bone	149	7	Fungus	+	*Aspergillus*
5666	8/M	N	2,000	AA	Y/Y	Sib-M	30	III	Blood	88	540+	N/A	–	*Candida*
5074	25/F	Y	2,000	HD/rel	N/Y	Auto	40	N/A	Skin	35	583+	N/A	–	*C albicans*

(*Continued on following page*)

3825	16/M	N	2,000	ALL/rel	Y/Y	HLA-lag	60	II	Liver	995	531+	N/A	−	*Candida*
5861	44/M	Y	2,000	CML/CP	Y/Y	Sib-M	40	0	Blood	11	63	Liver fail	−	*C albicans*
5711	48/M	Y	2,000	NHL/rel	Y/Y	Sib-M	20	III	Skin	90	5	Fungus	+	*Aspergillus*
5965	32/F	Y	2,000	NHL/rel	Y/N	URD	40	II	Lung	36	9	Fungus	+	*Aspergillus*
5990	30/F	Y	2,000	ALL/rel	Y/N	Sib-M	20	0	Blood	13	9	Fungus	+	*Candida*
5929	25/F	Y	2,000	AML/rem	Y/N	Sib-lag	40	II	Lung	58	46	Fungus	+	*Aspergillus*
6102	17/F	N	2,000	ALL/rel	Y/N	HLA-lag	20	0	Blood	59	4	Fungus	+	*C Tropicans*
5872	50/F	Y	2,000	AML/rel	Y/N	Sib-M	40	III	Blood	116	43	CMV	−	*Candida*
6109	46/M	Y	2,000	AML/rel	Y/N	Syng	30	II	Liver	13	72	Relapse	−	*Candida*
5912	30/F	Y	2,000	HD/rel	N/N	Sib-M	80	−	Lung	106	448+	N/A	−	*Aspergillus*
5832	31/M	N	2,000	CML/CP	N/Y	Sib-M	20	II	Sinus	150	10	Sepsis	+	Mold
6070	47/F	Y	2,000	MM/rel	N/N	Sib-M	30	II	Blood	15	69	ARDS	−	*Candida*
6099	19/M	N	2,000	AML/rel	Y/Y	URD	20	II	Blood	15	110	ARDS	−	*Candida*
6116	34/M	N	2,000	AML/rel	Y/Y	URD	20	III	Blood	54	4	Liver fail	+	*Candida*
5956	35/F	N	2,000	CML/BC	Y/Y	URD	40	III	Sinus	171	370+	N/A	−	*Aspergillus*
5976	25/F	Y	2,000	ALL/rem	Y/N	Sib-M	20	III	Lung	148	12	Fungus	+	*Aspergillus*
6171	30/F	Y	2,000	CML/AP	Y/N	URD	20	III	Lung	72	11	Fungus	+	*Aspergillus*

Abbreviations: ALL, acute lymphocytic leukemia; MM, multiple myeloma; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease; CML, chronic myelogenous leukemia; AA, aplastic anemia; FA, Fanconi's anemia; Rel, relapse, also includes CML in accelerated phase (AP) chronic, phase (CP), and blast phase (BP), Rem, remission; NA, not applicable (i.e., AA or MDS), TBI, total body irradiation; LAF, laminar air flow; Auto, autologous (6) or syngeneic (1); Sib, sibling; URD, unrelated donor; M, HLA matched; ×2, second transplant; lag, 1 HLA antigen mismatch; COD, cause of death; MOF, multi organ failure, CMV, cytomegalovirus, ARDS, adult respiratory distress syndrome; Y, yes; N, no; +, present; −, absent.

* Day of follow-up after initial dose of rhM-CSF; +, still alive on that day.

Table 2. Comparison of Characteristics Between rhM-CSF–Treated Patients and Historical Controls

	Historical Controls	rhM-CSF–Treated Patients 5/27/89–6/3/91
Dates qualified	1/29/88–5/26/89	5/27/89–6/3/91
Number patients	58	46
Median age (years)	32	31
Sex: male/female	34/24	28/18
Disease:		
AML/CML/ALL/NHL	13/10/14/6	13/7/10/7
MM/MDS/AA/HD/Nb	1/5/3/5/1	1/1/5/2/0
Disease state:		
relapse/remission/NA	29/11/8	28/5/6
CP/AP/BP	2/3/5	4/2/1
TBI: yes/no	40/18	33/13
LAF: yes/no	23/35	20/26
BMT type:		
sibling/unrelated/autologous	32/10/9	21/12/6
mismatch related/syngeneic/ NA	7/0/0	5/1/1
Karnofsky score:		
>20%/≤20%	38/20	30/16
Fungus type:		
Candida/Aspergillus/mold	43/14/1	30/15/1
Primary organ infected:		
blood/lung/liver	31/12/3	17/10/9
skin/central nervous system/bone	6/2/1	5/2/1
sinus/kidney	2/1	2/0
Pentoxifylline: yes/no	0/58	21/25

Abbreviation: Nb, neuroblastoma.

by evaluating all medical records from May 27, 1989, the date before the first patient entered into the rhM-CSF trial, to a random date of January 29, 1988. Consecutive patients who fulfilled the entry criteria as described above were used for the prospective rhM-CSF comparison.

Statistical analysis. Logistic regression was performed on categorical outcome variables (ie, cause of death, evaluation of fungus). Cox regression was performed on the continuous outcome variable (survival in days). Kaplan-Meier curves were produced for survival times across relevant predictor characteristics. All analyses were performed using the EGRET statistical package (Statistics & Epidemiology Research Corp, Software Division, Seattle, WA). Outcome variables included survival (continuous, days), cause of death (categorical, fungus/other), and evaluation of fungus on day of follow-up (categorical, fungus/no fungus). Predictor variables included age (continuous), sex (categorical, male/female), treatment with pentoxifylline (categorical, yes/no), maximum dose of rhM-CSF (continuous), BMT type (categorical, autologous/allogeneic), pre–M-CSF Karnofsky performance scores (continuous), pre–rhM-CSF Karnofsky performance scores (categorical, ≤20% >20%), GVHD (categorical, O-IV), organ of fungal involvement (categorical, blood/liver/other), fungus type (categorical, *Aspergillus/Candida*), disease, disease state, use of total body irradiation, use of laminar air flow room, and day post BMT of rhM-CSF administration. Variables other than rhM-CSF that significantly affected survival were identified for patients who received rhM-CSF, then comparison to historical controls was made controlling for the significant variables by Kaplan-Meier analysis. To increase the stringency of analysis the difference in overall survival was adjusted by Bonferroni adjustment.

RESULTS

Toxicity. Thrombocytopenia (reduction by more than 50%) was observed in 9 of the first 24 patients who received rhM-CSF. Thrombocytopenia occurred in 2 of the subsequent 22 patients (UPNs 5074, 5929) and both required a dose reduction of 50% (to 1,000 $\mu g/m^2/d$). Platelet counts remained low until rhM-CSF was discontinued; however, platelet counts did not decrease further after institution of the lower rhM-CSF dose. No other toxicity ascribed to rhM-CSF was observed.

Presence of fungal infection at day of follow-up evaluation. Twelve (87%) patients who did not survive 15 days had evidence of persistent fungal infection at the time of death (Tables 1 and 3). Patients who survived and received more than 2 weeks of therapy with rhM-CSF had a low incidence of fungal infection at time of follow-up (5/30, 17%). No patients who survived more than 150 days had documentation of recurrent fungal infection.

Survival. Cox regression using survival time in days as the outcome variable showed two significant independent predictor variables: Karnofsky performance scores ≤ 20% ($P < .001$; odds ratio = 6.97) and type of fungus (*Aspergillus*) ($P = .055$; odds ratio = 2.01) that were associated with lower survival. The logistic regression using evaluation of the presence of fungus at time of follow-up evaluation (present or not present) as the outcome variable also showed the same two significant predictors: Karnofsky performance scores of ≤20% ($P < .001$, odds ratio = 37.94) and *Aspergillus* infection ($P = .001$, odds ratio = 21.69). Survival of all patients who received rhM-CSF compared with historical controls is shown in Fig 1. Median follow-up of surviving patients who received rhM-CSF was 642 days (range 370 days to 903 days). Twelve patients remain alive and free of fungal disease. Thirty-four patients did not survive. The incidence of recurrence of malignancy was similar in the rhM-CSF–treated patients and the historical patients. Causes of death are shown in Table 1. The difference in overall survival was entirely because of better survival of patients with >20% Karnofsky score with invasive candidiasis. The survival of these patients compared with historical controls matched for similar Karnofsky performance scores and types of fungal infection is shown in Fig 2. A comparison of survival of rhM-CSF–treated patients to historical controls controlling for significant variables affecting survival is shown in Table 4. No difference in survival was observed in patients with ≤20% Karnofsky scores regardless of the type of fungal infection or in patients with *Aspergillus* infection regardless of the Karnofsky score. Other characteristics of rhM-CSF–treated patients and historical controls were similar (Table 2); however, 21 of the rhM-CSF patients received pentoxifylline during the past transplant course compared with none of the historical controls. This was not felt to affect the survival results because administration of pentoxifylline did not affect survival in patients who received rhM-CSF. Variables such as age, sex, maximum dose of rhM-CSF, type of BMT, GVHD, organ of fungal involvement, disease, disease state, use of total body radiation, use of laminar air flow room, and day of rhM-CSF administration also did not affect survival in patients who received rhM-CSF.

Table 3. Presence of Fungal Infection at Time of Evaluation

Days of Survival	Ratio (%) of Patients With Fungus at Day of Death or Last Follow-up Day
0–15	12/15 (87)
16–150	5/15 (33)
>150	0/15 (0)

The persistence of fungus was undetermined in one patient who did not undergo autopsy. He is not listed in this table.

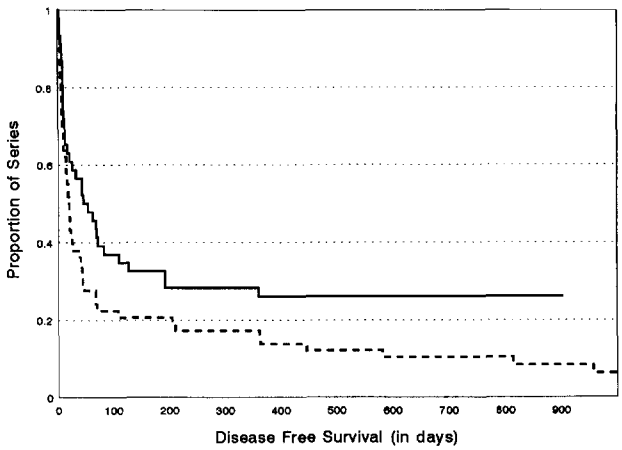

Fig 1. Survival by Kaplan-Meier analysis of 46 patients with invasive fungal infection who received rhM-CSF (——) compared with 58 historical controls (– –). Comparison was made using Mantel-Cox statistics; $P = .027$.

DISCUSSION

Overall, patients who received rhM-CSF had better survival then did historical controls or patients reported previ-

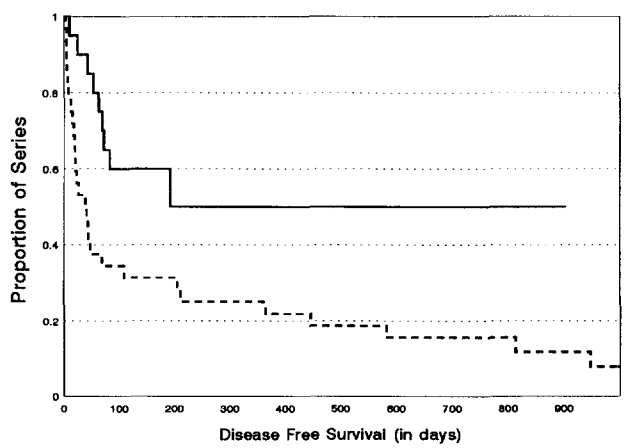

Fig 2. Disease-free survival by Kaplan-Meier analysis of 20 patients with Karnofsky scores > 20% and *Candida* (n = 19) or *Mucor* (n = 1) infection (——) who received rhM-CSF compared with 33 historical controls (– –) with the same Karnofsky scores and fungal infection (32 *Candida*, 1 *Mucor*). Both patients with *Mucor* died within 100 days after qualification. Comparison was made by using Mantel-Cox statistics; $P = .004$.

Table 4. Survival of Patients Who Received rhM-CSF Compared With Historical Controls

Group	>20% Karnofsky *Candida*	>20% Karnofsky *Aspergillus*	≤20% Karnofsky *Candida*	≤20% Karnofsky *Aspergillus*	Total
rhM-CSF	50% (n = 20)*	20% (n = 10)	0% (n = 11)	0% (n = 5)	27% (n = 46)
Control	15% (n = 33)*	0% (n = 5)	9% (n = 11)	0% (n = 9)	5% (n = 58)
P value†	.004	.675	.565	.228	.027
P value‡	<.05	ns	ns	ns	ns

Abbreviation: ns, not significant.

* Includes 1 patient with *Mucor* who did not survive as a result of progressive infection.

† Mantel-Cox analysis.

‡ Bonferroni adjustment.

ously.[8] However, the difference in overall survival was entirely because of a subset of treated patients with *Candida* infection and Karnofsky performance scores > 20%. Whether this is related to improved critical care techniques over time or the effect of rhM-CSF on monocyte/macrophage function awaits completion of an ongoing randomized, placebo-controlled trial. The majority of patients who survived long enough to receive the entire course of rhM-CSF did not develop recurrent fungal infection. These data suggest that the improved survival resulted from resolution of fungal disease. Potential beneficial activity of rhM-CSF may be a result of its functional enhancing capacity in monocytes and macrophages. Several in vitro studies have shown activation of monocyte and macrophage function with enhanced fungicidal activity after exposure to rhM-CSF.[11-14] Improved survival because of reduced mortality was also observed in *Candida*-infected mice and rats given rhM-CSF.[12,15] Enhanced function of monocytes occurs within 2 hours of administration of M-CSF in patients with lymphoma.[16] Some effects of M-CSF may also be via indirect mechanisms. rhM-CSF stimulates monocyte production of granulocyte CSF, granulocyte-macrophage (GM) CSF, interleukin-1, tumor necrosis factor-α, and interferon in vivo. These cytokines may further enhance cellular abilities to kill infecting organisms.[14] Determination of monocyte and/or macrophage function and circulating cytokine levels may identify patients likely or unlikely to respond to rhM-CSF or other growth factors.[17] rhGM-CSF may have similar antifungal properties to rhM-CSF,[18,19] whereas rhG-CSF is without affect.[20]

Results of this trial further substantiate those of the previously reported data and suggest that rhM-CSF is well tolerated at doses up to 2,000 $\mu g/m^2/d$. Reduction of the dose by 50% seems to minimize the severity of thrombocytopenia although the effects of the lower dose on functional enhancement of monocytes and macrophages may be reduced. Randomized placebo-controlled trials are needed to determine definitively the effect of rhM-CSF on resolution of fungal infection and survival.

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