Bone Marrow Transplantation for Children Less Than 2 Years of Age With Acute Myelogenous Leukemia or Myelodysplastic Syndrome

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We analyzed results of 40 infants less than 2 years of age who received bone marrow transplants (BMT) between May 1974 and January 1995 for treatment of acute myelogenous leukemia (AML; N = 34) or myelodysplastic syndrome (MDS; N = 6) to determine outcome and survival performance. Among the AML patients, 13 were in first remission, 9 were in untreated first relapse or second remission, and 12 were in refractory relapse. Patients were conditioned with cyclophosphamide in combination with either total body irradiation (TBI; N = 29) or busulfan (N = 11). Source of stem cells included 6 autologous donors, 15 HLA genotypically identical siblings, 14 haploidentical family members, and 5 unrelated donors. Graft-versus-host disease (GVHD) prophylaxis was methotrexate (MTX) for 17, MTX plus cyclosporine (CSP) for 14, or CSP plus prednisone for 3. Incidence of severe (grade 3-4) regimen-related toxicity was 10% and transplant-related mortality was 10%. Acute GVHD (grades II-III) occurred in 39% of allogeneic patients, and chronic GVHD developed in 40%. Relapse, the most significant problem for patients in this study, occurred in 1 MDS patient and 23 AML patients and was the cause of death for 19 patients. The 2-year probabilities of relapse are 46%, 67%, and 92%, respectively, for patients transplanted in first remission, untreated first relapse or second remission, and relapse. One MDS and 8 AML patients received second marrow transplants for treatment of relapse, and 5 of these survive disease-free for more than 1.5 years. All 6 MDS patients and 11 of 34 AML patients survive more than 1.5 years later. The 5-year probabilities of survival and disease-free survival are 54% and 38% for patients transplanted in first remission and 33% and 22% for untreated first relapse or second remission. None of the patients transplanted with refractory relapse survive disease-free. Outcome was significantly associated with phase of disease at transplantation and pretransplant diagnosis of extramedullary disease. Long-term sequelae included growth failure and hormonal deficiencies. Survival performance was a median of 100% (80% to 100%) and neurologic development for all survivors was appropriate for age. This study indicates that infants with AML have similar outcome after BMT compared with older children and that BMT should be performed in first remission whenever possible. In addition, allogeneic BMT provides effective therapy for the majority of infants with MDS.
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ALLOGENEIC BONE marrow transplantation (BMT) plays an important role in the primary therapy for children with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). Recent cooperative group studies have demonstrated superior outcome for patients with AML transplanted from matched related donors compared with those treated with chemotherapy alone.[1,2] For children who relapse after chemotherapy, BMT also offers a second chance for curative therapy.[3] Studies have also demonstrated favorable outcome for younger patients with MDS treated with allogeneic BMT.[4]

Outcome after marrow transplantation, tolerance of high-dose therapy, and risks for long-term sequelae may be different for very young children, who have distinct biologic and developmental characteristics to consider. We have previously reported outcome for a group of 11 children less than 2 years of age with AML transplanted in first complete remission.[5] These infants had favorable outcome with few early transplant-related problems, but follow-up was limited. In the present study, we update these results and expand our analysis to include 29 additional infants less than 2 years of age transplanted for AML or MDS referred to the Fred Hutchinson Cancer Research Center (FHCRC; Seattle, WA) for BMT.

PATIENTS AND METHODS

Between May 1974 and January 1995, 40 consecutive children less than 2 years of age with a diagnosis of AML or MDS received BMT at FHCRC or Children's Hospital and Medical Center (CHMC; Seattle, WA) and were analyzed as of December 1997. Diagnosis was made at the referring institution and confirmed by review of diagnostic bone marrow. Patient characteristics at diagnosis are shown in Table 1. The French-American-British (FAB) classification was used for assignment of disease subtypes M0 through M7 or refractory anemia with excess blasts (RAEB) and refractory anemia with excess blasts in transformation (RAEB/T).[6] Records of diagnostic cytogenetic analysis performed at referring institutions were available for 27 patients, with abnormalities reported for 21 AML patients and all MDS patients, 5 of whom had monosomy 7. Primary and secondary therapies for AML varied according to referring institution practice. Remission status was determined within 2 weeks before BMT by histopathologic analysis of bone marrow and cerebral spinal fluid (CSF) and cytogenetic analysis. Patients considered in untreated first relapse had histopathologic evidence for bone marrow relapse and were transplanted without further effort at remission induction.[7] Patients who received therapy for first relapse and achieved complete response in bone marrow (<5% blasts) and extramedullary sites of leukemia were considered to be in second remission, and those with greater than 5% marrow blasts or evidence of extramedullary disease despite remission induction were considered in refractory relapse.

Preparative regimens used for infants with AML or MDS depended on protocols in use at the time of transplant and were determined by phase of disease and type of donor (Table 2). From 1974 to 1982, total body irradiation (TBI) was delivered in a single setting of 9.2 to 10.0 Gy from opposing Co sources, and from 1982 onward 12.0 to 15.75 Gy TBI

Table 1. Patient Characteristics at Diagnosis

Characteristic	No. of Patients
Total no. of patients	40
Age (mo)	
Median	11
Range	1-21
Sex (M:F)	23:17
WBC ($\times 10^9$/L)	
Median	23.0
Range	1.0-227.0
EMD	
Total no. patients	11
Site	
CNS	8
Other	5
FAB classification	
M1/2	1/5
M4/M5	8/13
M7	7
RAEB/RAEB-T	5/1
Cytogenetics	
Normal	3
Monosomy 7	5
Abnormal 11(q23)	10
Other cytogenetic abnormality*	9
Unknown	13

*Hyperdiploidy (n = 2); trisomy 8 (n = 1); trisomy 21 (n = 1); isochrome 8 (n = 1); deletion 9q (n = 1); multiple complex abnormalities (n = 3).

was delivered in fractionated or hyperfractionated doses as previously described.[5,8,9] Eleven infants were prepared with busulfan (Bu) plus cyclophosphamide (Cy) and did not receive TBI. Intrathecal methotrexate (MTX) was administered during the preparative phase to 25 patients who had either history or presence of central nervous system (CNS) disease. Four patients with CNS leukemia at the time of transplant received 6.0 to 23.0 Gy irradiation to the CNS and 2 patients with testicular leukemia received 5.0 and 10.0 Gy testicular irradiation immediately before the start of conditioning. Beginning in 1990, 5 patients received posttransplant consolidation with interleukin-2 (IL-2).[10,11] Transplant protocols and consent forms were approved by the Institutional Review Board (IRB) at FHCRC or CHMC, and informed consent was obtained from parents or guardians according to IRB policies.

Histocompatibility testing was performed by the Clinical Immunogenetics Laboratory at FHCRC for all patients and donors. The standard National Institute of Health (NIH) two-stage microtoxicity assay[9] was used for typing of HLA-A and -B antigens, assigned as defined by the World Health Organization (WHO) HLA nomenclature committee.[12] HLA-DR typing was performed using nylon wool-purified B lymphocytes in a modified microtoxicity assay, and compatibility of HLA-D region was defined by determining Dw phenotype using HLA-D homozygous typing cells (HTC).[9,12] From 1990, HLA-D region compatibility was determined by identification of DRB1 alleles through hybridization of sequence-specific oligonucleotide probes (SSOP).[13] Patient-donor compatibility was further tested by lymphocyte crossmatch (patient serum v donor T and B cells) before transplantation.[14] Mismatched related donors were matched for HLA-A, -B, and -DR/DRB1 on one haplotype and could be mismatched for one to three HLA-A, -B, or -DR/DRB1 antigens on the second haplotype. Unrelated donors were either matched for HLA-A, -B, and -DR/DRB1 or had incompatibility of a single HLA locus, defined as a disparity within a cross-reactive group for the HLA-A or -B loci or within the same

serologically defined DR specificity, for HLA-Dw antigens or DRB1 alleles.

All allogeneic transplant recipients received unmanipulated bone marrow cells collected according to established methods.[8,15] One patient also received allogeneic peripheral blood stem cells (PBSC) mobilized with a 6-day course of granulocyte colony-stimulating factor (G-CSF; 10 mg/kg).[16] Among the autologous patients, 3 received marrow purged with 4-hydroperoxycyclophosphamide (4HC), 2 received nonpurged marrow plus PBSC, and 1 received PBSC alone. Stem cell products were infused through a central venous catheter on day 0, at least 36 hours after last dose of preparative chemotherapy or within 24 hours after the last dose of irradiation. Recipients of allogeneic marrow received prophylaxis for graft-versus-host disease (GVHD) depending on type of donor and protocol in use at time of BMT, as shown in Table 2.[8,17]

All patients had indwelling central venous catheters. Nutritional support was provided by hyperalimentation. Measures to prevent infection varied according to the standard of practice at the time of BMT, including prophylactic fluconazole[18] and ganciclovir for cytomegalovirus (CMV) prophylaxis,[19,20] as well as use of single conventional or laminar airflow rooms, growth factors, and intravenous Ig.

Engraftment was defined by achievement of peripheral granulocyte count of greater than 500/μL for 3 consecutive days and by donor cytogenetics. Patients were not considered evaluable for engraftment if they died and did not achieve a granulocyte count greater than 500/μL before day 28. For allogeneic recipients, donor engraftment was determined by in situ DNA hybridization with Y-body–specific probe[21] (sex-mismatched transplants), by restriction fragment length polymorphism (RFLP) analysis,[22] or by polymerase chain reaction (PCR) assay of genomic DNA for variable number of tandem repeats (VNTR).[23] Regimen-related toxicity (RRT), including veno-occlusive disease (VOD), was scored using the method of Bearman et al.[24] Criteria for skin toxicity were modified to include perianal skin toxicity (dermatitis) defined as grade 1 for a rash and grade 2 for epidermal erosion. Acute and chronic GVHD were diagnosed according to conventional criteria and treated as previously described.[8,25,26] Patients were not considered evaluable for acute GVHD if they died before engraftment. Patients were not considered evaluable for chronic GVHD if they died before day 80. Quality of life was evaluated by using the Lansky Play Performance Scale (LPPS) results reported by parent/guardians or physicians on an annual basis.[27] Growth was evaluated by annual reports of height measurements and height standard deviation (SD) scores, calculated as the difference between the 90th and 10th percentiles for a given age and gender, divided by 2.56[28] (GrowTrak; Genetech, Inc, South San Francisco, CA). Annual evaluation for hormonal deficiency included measurement of growth hormone (GH), thyroxine (T4), thyroid stimulating hormone (TSH), luteinizing hormone (LH), and follicle stimulating hormone (FSH). Neuropsychologic development was evaluated using Full Scale Intelligence Quotient (FSIQ) tests appropriate for age at testing.[29,30]

Statistical methods. Proportional hazards regression models were fit for the endpoints overall survival, relapse, and disease-free survival (DFS; death or relapse, whichever occurs first, is considered an event). For each of these endpoints, data from all 40 patients were used when examining explanatory variables relevant to patients with AML or MDS. When variables relevant only to patients with AML were examined, regression models were restricted to data from the 34 patients with this diagnosis. Explanatory variables examined included donor age, patient gender, extramedullary disease (EMD; defined as diagnosis of EMD at any time before transplantation), cytogenetic abnormalities (examined in two ways: normal v abnormal and normal v abnormal involving chromosome 11q23 v abnormal not involving chromosome 11q23), white blood cell count (WBC) at diagnosis (WBC >20.0 v <20.0), phase of disease at transplant (early phase AML [defined as first remission] v intermediate stage AML [defined as

Table 2. Patient Characteristics at Time of Transplantation

	Donors			
	0-1 Antigen Related Mismatched	2-3 Antigen Related Mismatched	Unrelated	Autologous
Total no. of patients	21	8	5	6
Age (mo)				
Median	20	16	21	19
Range	10-24	11-24	12-24	5-24
Diagnosis to transplant (mo)				
Median	4	7	7	9
Range	3-22	3-13	4-9	5-11
Phase of disease				
MDS	2	3	1	—
CR1	10	—	1	2
CR2	2	—	—	2
Untreated 1st relapse	3	—	—	2
Relapse	4	5	3	—
History of EMD				
Total no. of patients	7	3	1	4
Site				
CNS	7	2	1	4
Other	2	2	1	3
CMV				
(+) recipient/(±) donor	4	3	2	2
(−) recipient/(+) donor	3	1	1	—
(−) recipient/(−) donor	8	4	2	4
Unknown	6	—	—	—
Regimen				
Cy + TBI 10.0 Gy*	6	—	—	—
Cy + TBI 12.0-15.75 Gy†	8	8	4	3
Bu + Cy‡	7	—	1	3
GVHD prophylaxis				
MTX	16	—	1	—
MTX/CSP	3	8	3	—
Other§	2	—	1	—
Engraftment (evaluable)	20 (21)	7 (7)	4 (5)	5 (5)
Acute GVHD (evaluable)	(20)	(7)	(4)	—
0-I	17	2	—	—
II	2	2	3	—
III	1	3	1	—
Chronic GVHD (evaluable)	2 (11)	3 (5)	3 (4)	—
Relapse after BMT	12	5	3	4
Day after BMT median (range)	113 (35-347)	60 (21-364)	87 (79-416)	136 (59-420)
Disease-free survivors (%)	8 (38%)	2 (25%)	1 (20%)	1 (17%)
Survivors (%)	10 (48%)	3 (38%)	2 (40%)	2 (33%)

Abbreviations: CR1, first complete remission; CR2, second complete remission; CSP, cyclosporine; Cy, cyclophosphamide.

*Cy (120 mg/kg); 1 patient also received Bu (50 mg).

†Cy (120 mg/kg); 6 patients received Cy (60 mg/kg) + Bu (8 mg/kg); 1 patient received Cy (40 mg/kg) + Cytarabine (3,000 mg/m²).

‡Bu (16 mg/kg) + Cy (200 mg/kg); 1 patient received Bu (18 mg/kg); 1 patient received Bu (24 mg/kg).

§CSP + Prednisone or CSP alone.

untreated first relapse or second remission] *v* advanced stage AML [defined as relapse] *v* diagnosis of MDS), type of transplant (autologous *v* matched related *v* mismatched or unrelated), patient and donor CMV serostatus, use of TBI, and GVHD prophylaxis (autologous *v* CSP + MTX *v* others). Estimates of overall survival and DFS were calculated using the method of Kaplan and Meier,[31] and cumulative incidence estimates were used to describe relapse rates.[32] For the endpoint of relapse, death without relapse was regarded as a competing risk. In the regression models, patients not reaching the appropriate endpoint were censored at last contact or failure from a competing risk, whichever occurred first. All *P* values associated with the regression models were derived from the Wald test and are two-sided. Comparisons between proportions of patients with a specific characteristic were made using the

Fischer's exact two-sided test. No adjustments were made for multiple comparisons.

RESULTS

Patient characteristics. Patient characteristics at time of transplant are shown in Table 2. Twenty-one of the 34 patients with AML had disease phase beyond first remission at time of transplant. Of the 13 patients transplanted in first remission, 9 had one or more poor prognostic factors, including WBC greater than 20.0×10^9/L at diagnosis in 5, history of extramedullary disease in 3, or 11q23 cytogenetic abnormality in 2. EMD was diagnosed in 15 AML patients before transplan-

tation, 6 of whom had more than one site involved. Sites of EMD included CNS in 14 patients, skin in 4, testes in 2, mastoid bone in 1, and orbit in 1. Four patients who developed EMD before BMT did not have EMD at diagnosis of AML. Of the 11 patients with EMD at diagnosis, 4 had no recurrence before BMT and 7 had recurrence of EMD at the same site. Six AML patients and 2 MDS patients were less than 1 year of age at BMT, and 6 of these 8 patients were conditioned with TBI. Fourteen donors were genotypically HLA-identical siblings. Haploidentical family donors included 1 phenotypically HLA-identical, 6 mismatched for one antigen, 4 mismatched for two antigens, and 4 mismatched for three antigens. Of the 5 unrelated donors, 3 were determined to have mismatch for one antigen.

Survival and DFS. All 6 infants with MDS survive greater than 1.5 years after BMT. One of these relapsed with AML and survives after second BMT, and the rest survive continuously disease-free. Eleven of the 34 infants with AML are surviving more than 1.5 years after BMT. Nineteen patients died from recurrent leukemia and 4 patients died of causes other than relapse. Overall survival and DFS are shown in Table 2.

Results from univariable regression models are contained in Table 3. Diagnosis and stage of disease were statistically significantly associated with the hazard of mortality (survival) as well as the hazard of death or relapse (DFS). The association of stage of disease with survival among patients with AML is shown in Fig 1. None of the 6 patients with MDS has died as of last contact; thus, the relative risk of death cannot be determined. History of EMD was also significantly associated with survival and DFS (Table 3 and Fig 2). Only 2 of the 15 patients who developed EMD before BMT survive long term (10 of these died of relapse and 3 died of other causes), whereas 9 of 19 AML patients without EMD survive long term.

No other variables were significantly associated with the survival or DFS, although the relatively small number of patients prevents definitive conclusions. Six of the 11 patients conditioned with BuCy survive long-term (3 of these without recurrent disease), and 11 of 29 patients conditioned with TBI survive long-term (9 of these without recurrent disease). Both autologous patients transplanted in first remission survive, whereas none of the 4 autologous patients transplanted in untreated first relapse or second remission survive.

When attempting to fit a multivariable model for survival and DFS for all patients, no variables were significantly associated with the appropriate hazard once stage of disease was considered. However, among AML patients, the same was true of EMD. Because the number of patients in this study is relatively small, it is not possible to determine whether these variables act independently, synergistically, or interchangeably.

Relapse. Relapse occurred in 24 patients: 23 with AML and 1 with MDS. Results from univariable regression analyses are provided in Table 3. Stage of disease was significantly associated with relapse, and history of EMD was suggestive of being associated with relapse.

Preparative regimen was not found to be significantly associated with relapse. This may be misleading, because phase of disease was not equivalent between the BuCy- and TBI-treated groups. Among AML patients transplanted in first or second remission or untreated first relapse, relapse occurred in 7 of 10

Table 3. Univariable Regression Models

Variable	P Value	Overall Survival	
		Relative Risk	95% CI
Disease status*			
AML—CR1	—	1.0	—
AML—CR2, RELU	.580	1.38	0.44-4.28
AML—REL	.014	3.61	1.30-10.02
MDS	—	—	—
EMD†			
No	—	1.0	—
Yes	.055	2.26	0.98-5.20

Variable	P Value	DFS	
		Relative Risk	95% CI
Disease status‡			
AML—CR1	—	1.0	—
AML—CR2, RELU	.445	1.49	0.54-4.13
AML—REL	.037	2.67	1.06-6.70
MDS	.121	0.19	0.02-1.54
EMD§			
No	—	1.0	—
Yes	.030	2.36	1.09-5.14

Variable	P Value	Relapse	
		Relative Risk	95% CI
Disease status‖			
AML—CR1	—	1.0	—
AML—CR2, RELU	.359	1.70	0.55-5.32
AML—REL	.019	3.45	1.23-9.66
MDS	.194	0.25	0.03-2.04
EMD¶			
No	—	1.0	—
Yes	.080	2.12	0.92-4.93

Abbreviations: CR1, first complete remission; CR2, second complete remission; REL, relapse; RELU, untreated first relapse; 95% CI, 95% confidence interval.

*Likelihood ratio test for entering presence of EMD into this model yields $P = .24$.

†Among AML patients only; likelihood ratio test for entering stage of disease into this model yields $P = .11$.

‡Likelihood ratio test for entering presence of EMD into this model yields $P = .14$.

§Among AML patients only; likelihood ratio test for entering stage of disease into this model yields $P = .34$.

‖Likelihood ratio test for entering presence of EMD into this model yields $P = .43$.

¶Among AML patients only; likelihood ratio test for entering stage of disease into this model yields $P = .05$.

conditioned with BuCy and 5 of 12 conditioned with TBI. All 12 patients with refractory relapse were conditioned with TBI, and relapse occurred in 11. Type of donor also was not found to be significantly associated with relapse; however, again, phase of disease was not evenly distributed between the autologous and allogeneic patients. Among the group of patients transplanted in first or second remission or untreated first relapse, relapse occurred in 4 of 6 patients receiving autologous marrow and 8 of 16 receiving allogeneic marrow. None of the 12 patients with refractory relapse received autologous marrow.

If stage of disease alone is included in a regression model, no other variable provides a statistically significant improvement to this model. In particular, the likelihood ratio test for addition
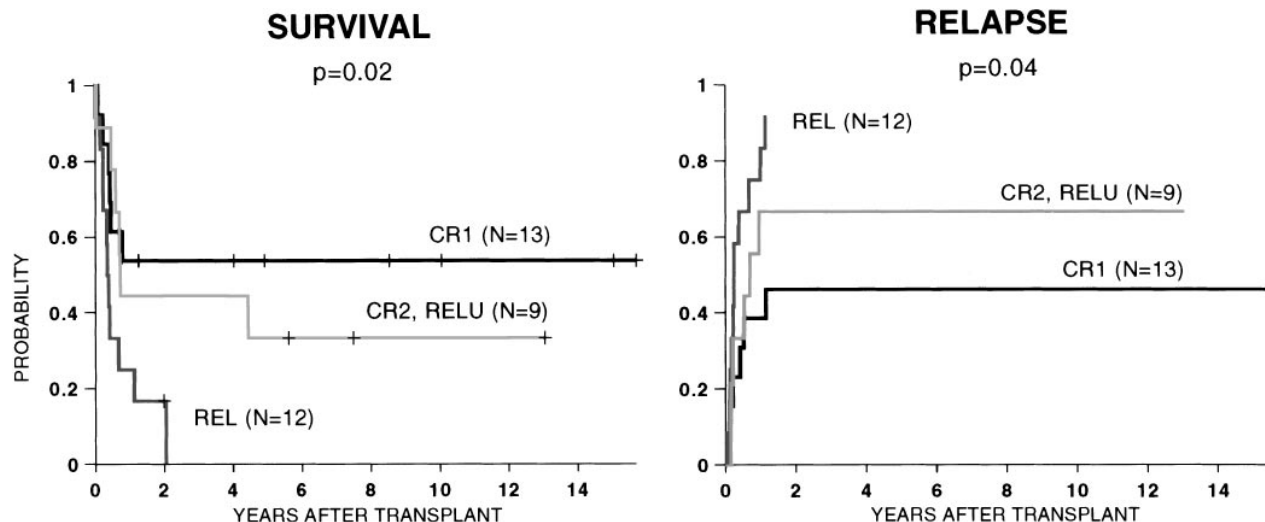
SURVIVAL

p=0.02

RELAPSE

p=0.04

Fig 1. Kaplan-Meier estimates of survival (left panel) and cumulative incidence estimates of relapse (right panel) for 34 patients with AML stratified for phase of disease at BMT. Statistical significance was determined by log-rank test.

of EMD yields $P = .43$. On the other hand, addition of stage of disease to the model already containing EMD yields $P = .05$, suggesting that the impact of relapse on outcome is not entirely accounted for by the impact of having EMD. However, similar to survival and DFS, the small number of patients limits the power to detect anything but relatively large differences.

Engraftment. Thirty-six patients achieved sustained engraftment. Two patients died before engraftment could be evaluated, 1 from disseminated fungal infection on day 5 and 1 from cardiac arrhythmia on day 12. Graft failure occurred in 2 patients. One patient with M1 AML in first remission received 6.5×10^8 mononuclear cells (MNC)/kg marrow from his father, who was mismatched for one antigen at the DR locus. Patient serum did not react with donor lymphocytes pretransplant; however, after transplant, antibodies against donor B cells were demonstrated. Engraftment was achieved after a second marrow

infusion from the same donor after a preparative regimen using Cy/ATG, but the patient died from relapse on day 165. One patient with M7 AML in first remission received 2.3×10^8 MNC/kg from a phenotypically matched unrelated donor after BuCy conditioning, but died from infection with persistent graft failure 21 days after a second marrow transplant from a different matched unrelated donor after a CyTBI conditioning regimen.

RRT. Information regarding toxicities resulting from the conditioning regimen was available for 37 infants (Table 4). Two infants died of noninfectious causes during the first 30 days after transplant, 1 from cardiac arrhythmia and 1 from a medication error. The fatal cardiac event occurred in an infant with a previous history of cardiomyopathy and a pretransplant ejection fraction of 32%. Grade 3 toxicities included mucositis resulting in temporary intubation for airway obstruction in 2 patients and reversible renal failure in 1 patient who required
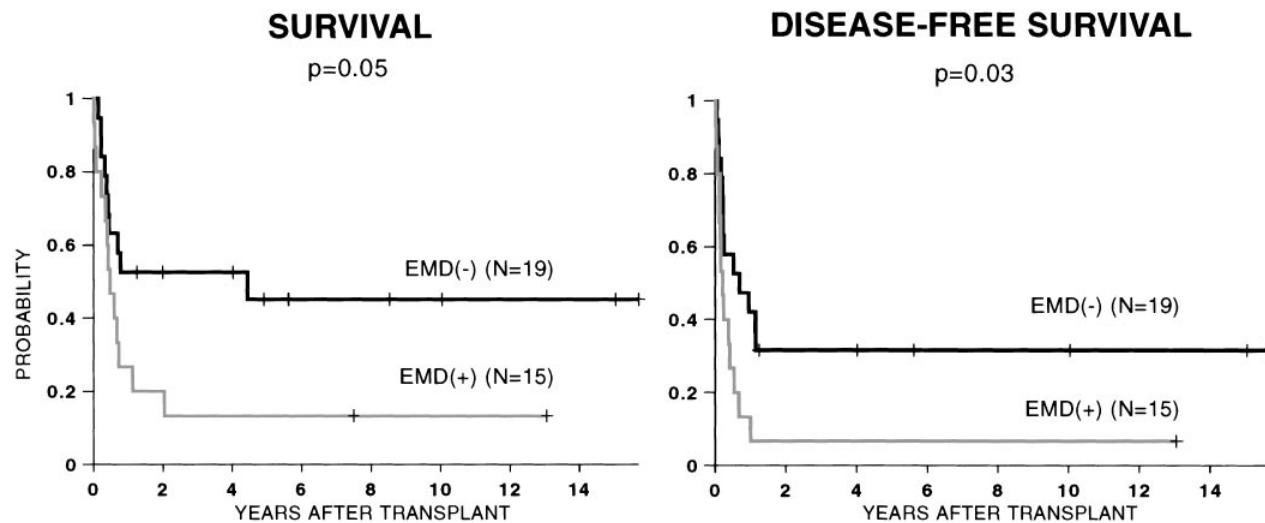
SURVIVAL

p=0.05

DISEASE-FREE SURVIVAL

p=0.03

Fig 2. Kaplan-Meier estimates of survival (left panel) and DFS (right panel) for 34 patients with AML stratified for history of EMD before BMT. Statistical significance was determined by log-rank test.

Table 4. RRT for 34 Infants With AML or MDS

Toxicity	No. of Patients	Grade			
		1	2	3	4
Mucositis	34	11	21	2	—
Dermatitis	15	13	2	—	—
GI	11	5	6	—	—
Cystitis	9	7	2	—	—
Hepatic*	8	6	2	—	—
Pulmonary	8	5	3	—	—
Cardiac	3	1	1	—	1
Renal	1	—	—	1	—
CNS	0	—	—	—	—

*VOD.

transient dialysis. Grade 1-2 mucositis and dermatitis were the most frequently observed toxicities. Perianal skin breakdown (diaper dermatitis) accounted for 8 of 15 cases of skin toxicity, occurred in association with diarrhea, and generally persisted until granulocyte recovery. Hepatic toxicity (VOD) was limited in severity (grades 1-2) with maximum bilirubin of 0.8 to 6.0 mg/dL and weight gain of 5% to 11% over baseline. All cases of hemorrhagic cystitis resolved within 10 days without intervention other than platelet support. Two patients developed transient episodes of congestive heart failure treated with diuretics. Three patients required temporary supplemental oxygen for pulmonary toxicity that could not be explained by infection.

RRT were analyzed according to conditioning regimen and diagnosis. Comparing available data for 11 patients who received BuCy to 26 TBI patients, the incidence and severity of mucositis, VOD, and pulmonary toxicity were similar. Recipients of BuCy had an apparent decrease in incidence of diarrhea (8% v 42%, P = .02) and perianal skin breakdown (0% v 27%, P = .08). No grade III or IV toxicities or cardiopulmonary complications were observed in the MDS patients.

GVHD. Acute GVHD developed in 17 of the 31 evaluable allogeneic patients. Grades II-III acute GVHD occurred in 9 patients with AML and 3 patients with MDS, for an overall incidence of 39%. Of the 4 patients who developed grade III GVHD, 1 received marrow from a matched sibling donor and 3 received marrow from unrelated or mismatched related donors. No patient developed grade IV acute GVHD and there were no deaths resulting from acute GVHD. Eight of 20 infants who survived more than 80 days after allogeneic BMT developed chronic GVHD. GVHD resolved in 6 patients after a single 9-month course of immunosuppresive therapy, and 2 patients required further treatment of 3 and 18 months' duration. No patient died from opportunistic infection, bleeding, or other condition associated with chronic GVHD, and no patient has ongoing chronic GVHD requiring therapy.

Long-term side effects. Information regarding growth and development was available for all 17 long-term survivors, including 4 patients who survive into puberty. For the first 2 years after BMT, growth velocity and height SD scores were within normal ranges for all patients (Fig 3). Growth rate and height SD scores for the 3 patients who received BuCy continued to remain within the normal range, with follow-up of 3 to 6 years. In contrast, the 14 patients who received TBI developed growth failure beginning approximately 3 years after BMT, at which time height SD scores decreased to less than

−2.0. Although small numbers of patients prevent definitive conclusions, there were no apparent differences in height SD scores related to age at BMT (<13 [N = 5] v >13 months [N = 9]), type of irradiation (single [N = 3] v fractionated dose TBI [N = 11]), number of transplants (1 [N = 10] v 2 [N = 4]), or history of cranial irradiation (N = 2). Information regarding hormonal status was available for 14 long-term survivors (Table 5). Growth hormone deficiency developed in 6 of 7 patients tested at least 3 years after BMT, all within the group who received TBI. Five of these patients were treated with recombinant growth hormone that resulted in improved height SD scores for 3 patients who received therapy before onset of puberty. Height SD scores for 2 patients treated with growth hormone after puberty did not improve. Thyroid hormone production was evaluated annually in 13 patients and 2 patients have developed thyroid hormone deficiency at 10 and 13 years after transplant. Both patients received a single 10.0 Gy dose of TBI. Among the 4 patients who reached more than 12 years of age, 2 have developed primary gonadal failure with elevated LH and FSH and deficient sex hormone production and 2 have not been evaluated.

Fourteen long-term survivors, including 4 patients less than 1 year of age at BMT, had LPPS scores of 100%, a measurement of survival performance after BMT. Two patients had LPPS scores of 90%, 1 of whom was 9 and 13 months of age, respectively, at first and second BMT. One patient who received a second transplant and developed chronic GVHD had an LPPS score of 80%. Eleven patients have reached school age, and all
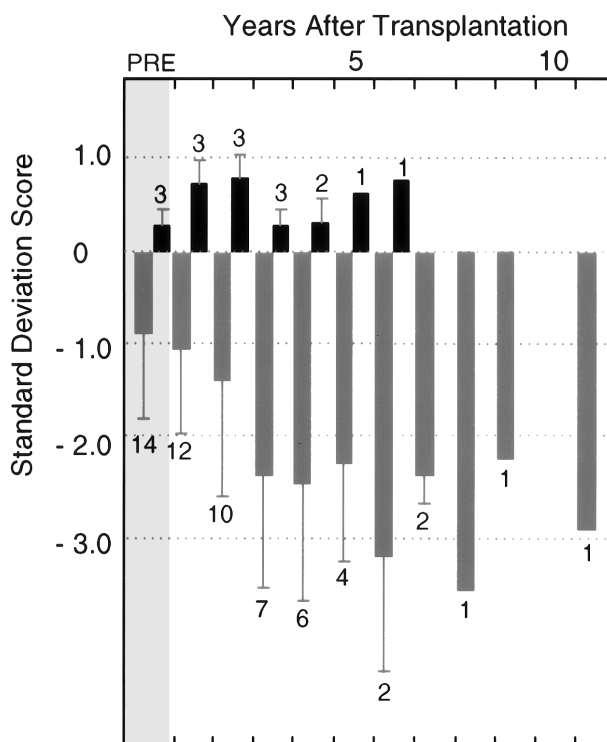

Fig 3. Mean height SD scores plotted for each year after transplantation, grouped separately according to whether patients were conditioned with TBI (▨) or BuCy (■). The number of patients tested at each time point is given next to the error bar. Patients were censored after initiation of exogenous growth hormone therapy.

Table 5. Endocrine Function in 14 Patients Transplanted Before 2 Years of Age

UPN	Sex	Tx Age*	Current Age	TBI (cGy)	GH Deficient (age)	Thyroid Deficient (age)	Sex Hormone Deficient (age)
1227	F	1.9	19.4	1,000†	Y (6.3)	Y (13.1)	Y (13.4)
1235	M	1.5	19.0	1,000†	Y (13.0)	Y (10.8)	Y (13.0)
1920	M	1.0	16.0	1,575	Y (9.4)	N	NT
4054	*F*	*0.8/1.1*	*11.1*	*1,575‡*	*Y (5.4)*	*N*	*NT*
4654	*M*	*1.8/2.1*	*11.6*	*1,575‡*	*Y (4.0)*	*NT*	*—*
5570	M	1.0	8.6	1,440	NT	N	—
5792	M	1.5	8.9	N	N (3.9)	N	—
6128	*F*	*0.4/1.7*	*7.0*	*1,440*	*Y (5.9)*	*N*	*—*
6813	M	1.7	7.5	N	NT	N	—
6903	M	0.9	6.4	1,200	Y (1.9)	N	—
8040	M	1.8	5.8	1,200	NT	N	—
8218	*F*	*1.4/3.0*	*4.1*	*1,440*	*NT*	*N*	*—*
9255	F	1.2	4.5	1,200	Y (2.8)	N	—
9609	M	1.2	3.7	1,440	N	N	—

Abbreviations: UPN, unique patient no.; Tx, transplant; NT, not tested; Y, yes; N, no.

*Patient age (in years) at first or first/second transplant. Patients who received second transplants are italicized.

†TBI delivered as single dose.

‡Patient also received cranial irradiation.

have progressed in school at appropriate grade levels. FSIQ was measured for 5 AML patients between 3 and 12 years of age. FSIQ scores were 117 and 78, respectively, for 1 patient conditioned with fractionated TBI at age 12 months and 1 patient conditioned with single-dose TBI at age 18 months. FSIQ scores for 3 patients who received second BMTs were 81, 89, and 101, respectively, with the last two scores reflecting patients also treated with cranial irradiation.

Three patients developed other long-term sequelae. One patient developed asymptomatic cataracts at 4 years of age. A second patient developed congestive heart failure (stable with digoxin therapy) and hepatitis C virus hepatitis at 7 and 8 years after BMT, respectively. The third patient developed a bipolar disorder 16 years after BMT, requiring psychiatric hospitalization.

Second marrow transplant. Eight of the 23 AML patients who relapsed after first transplant were treated with a second marrow transplant and 1 of these also received a third. One MDS relapsed with AML 82 days and received a second BMT at another institution while in remission after chemotherapy. Conditioning regimen, donor, and outcome are shown for second transplant patients in Table 6. Four of the 8 patients who received a second BMT for recurrent leukemia remain alive without disease more than 2.5 years after first BMT, 3 died of relapse, and 1 died of toxicities associated with second BMT. None of the 15 patients who did not receive a second BMT survives.

DISCUSSION

Despite intensive chemotherapy less than half of all children with AML will survive.[33,34] Infants with AML are more likely than older children to have aggressive disease associated with inferior outcomes.[35] The current study found phase of disease at time of transplant to be an important prognostic factor for survival and relapse. Infants who received BMT in first remission had significantly better overall survival and a significantly lower rate of relapse compared with infants transplanted in more advanced phases of disease. Prospective cooperative group studies in newly diagnosed AML patients have consistently shown better outcome for patients receiving allogeneic transplants in first remission compared with those receiving chemotherapy alone, with DFS of 50% to 60% verus 30% to 40%.[1,2,36] However, none of these studies specifically addresses comparative outcome for infants. Our series of infants transplanted in first complete remission shows similar overall survival of 54% but an apparent lower DFS of 38%, which may reflect the aggressive nature of infant AML and/or inclusion of a high proportion of patients with poor prognostic factors. For infants with disease beyond first remission, BMT was successful only if performed in untreated first relapse or second complete remission. Of this group, 4 of 9 infants survive long term, 1 after second BMT. Results in the current study are comparable to larger series of older children transplanted in second remission, in which DFS of 37% DFS and relapse risk of 48% have been reported.[37] Other studies have reported DFS of

Table 6. Second Marrow Transplants

UPN	Regimen	Donor	Day of Relapse	Day of 2nd BMT	2nd Regimen	2nd Donor	Survival From 2nd BMT (yr)	COD After 2nd BMT
3318	TBI	MMR	364	378	BuCy	MMR	1.0	Relapse
3509	BuCy	MMR	347	363	TBI	MMR		—
3509*	—	—	573†	944†	BCV	MMR	3.5†	Relapse
4054	BuCy	MR	78	100	TBI	MR	>8.2	—
4654	BuCy	MR	52	105	TBI	MR	>7.2	—
6128	BuCy	AUTO	420	490	TBI	MMR	>3.5	—
6805	BuCy	MMR	189	234	TBI	MMR	0.2	VOD
7426	TBI	MMR	82	819	?‡	MMR	>2.5	—
7915	BuCy	AUTO	59	90	TBI	URD	0.1	Relapse
8218	TBI	URD	416	558	BuTh	URD	>1.9	—

Abbreviations: COD, cause of death; BCV, cyclophosphamide, etoposide, and carmustine; BuTh, busulfan + thiotepa; MMR, mismatched related donor; MR, matched related donor; URD, unrelated donor; AUTO, autologous.

*Third transplant.

†Interval relative to first BMT.

‡Second transplant performed at another institution.

61% to 75% for second remission patients treated with allogeneic[3] or autologous BMT[38] using preparative regimens similar to those in the current study. The small numbers of patients in these studies preclude comparison; however, the fact that these outcomes were not observed in the current study may reflect the difficulty of eradicating recurrent leukemia in infants. Correspondingly, outcome for infants with disease beyond second remission was extremely poor. Despite lower transplant-related mortality, infants with advanced disease did not have a better outcome than older patients.[39,40] Thus, the current study supports allogeneic marrow transplant for treatment of infants in first remission.

EMD was the only other factor statistically significantly associated with poor outcome in our series. Among the 44% of AML patients with a history of EMD before transplantation, DFS was 7%, compared with 32% for infants without EMD. Outcome for infants is comparable to that observed for older children with EMD, for whom a DFS of less than 15% after either conventional chemotherapy or BMT has been reported.[33] EMD should be considered as a prognostic factor in addition to phase of disease at transplant, even though our small number of patients precludes definitive determination of whether these variables act independently to influence outcome. Poor outcome for infants with EMD was due to relapse; thus, efforts to improve DFS for this group of patients should be directed toward decreasing recurrent leukemia.

The primary cause of treatment failure for infants in this study was relapse. To improve outcome our results suggest, first, that the optimum time to transplant infants is in first remission, based on the significantly smaller risk for relapse. Secondly, for patients transplanted after first remission, the primary strategy for improving survival should be directed toward decreasing incidence of posttransplant relapse. Methods to reduce disease recurrence include use of more intensive transplant preparative regimens[41] or posttransplant immune modulation, such as IL-2.[11] Additionally, aggressive pretransplant induction therapy has been shown to improve outcome after BMT for first remission patients, probably by minimizing leukemic burden before the transplant preparative regimen.[42] However, further intensification of the induction regimen appears to be limited by toxicity-related deaths, reported to be at least 10% in current investigations, precluding marrow transplantation for a significant number of patients.[42] We have previously demonstrated that intensification of the transplant regimen results in fewer relapse-related deaths for patients with acute leukemia.[41] However, in most studies, the benefit of an intensified regimen is offset by the increased incidence of toxic deaths.[41,43,44] In the current study, the incidence of regimen-related mortality was relatively low, suggesting that infants may be a group of patients who will better tolerate more aggressive preparative regimens. Novel methods to deliver increased doses of therapy while avoiding additional toxicity, such as dosing Bu based on therapeutic blood levels[45] or use of radiolabeled monoclonal antibody targeted to hematopoietic cells,[46] are currently being developed in our institution for use in young children.

Posttransplant immune modulation might also improve outcome for infants at risk of relapse. Graft-versus-leukemia (GVL) has been implicated in reduction of relapse rates observed in larger series of patients with AML receiving marrow from mismatched or unrelated donors.[47,48] Because infants have a low risk of complications from GVHD and a high risk of relapse, we are currently exploring strategies to increase GVL effects. Outcome of mismatched related or unrelated donor grafts is similar to that of genotypically identical donors in the study presented here; thus, alternative donors should be considered for infants at high risk of relapse without an HLA-identical sibling who would otherwise benefit from transplantation in first remission. Reducing the strength of GVHD prophylaxis also may enhance GVL, an approach that appears to benefit patients in first relapse being grafted from HLA-identical siblings.[44,49] Thus, we consider MTX alone to be sufficient GVHD prophylaxis for infants, particularly for those with genotypically identical donors. Furthermore, we are currently exploring strategies for induction of GVL in infants who do not develop GVHD. Phase I studies of posttransplant IL-2 immunotherapy have demonstrated that it can be given safely to children and may decrease the relapse rate if administered early after BMT.[10,11] The effect of donor lymphocyte infusions in patients without significant GVH who develop cytogenetic relapse is also being investigated.[50]

Infants who relapsed after transplant died from their recurrent leukemia, except for some infants receiving a second BMT. Second marrow transplants resulted in long-term survival for 50% of patients, an outcome comparable to that reported previously for children less than 10 years of age.[51] Infants initially conditioned with either BuCy or TBI had similar outcomes after second BMT, although small numbers make comparison difficult. Infants initially conditioned with BuCy tolerated their second transplant as early as 3 months after the first. Significant toxicity was not observed for second transplants after initial TBI-conditioned BMT, a situation that is benefited by a longer interval between transplants.[51] Relapse continued to be the major cause of death after second transplant.

This study demonstrates that risk for regimen-related mortality after transplant is low (<10%). Half of the regimen-related deaths occurred in infants with pre-existing conditions, ie, cardiac death in a patient with cardiomyopathy and infectious death in a patient with pre-existing infection. Growth failure associated with growth hormone deficiency was the most frequent long-term sequelae observed in patients conditioned with irradiation.[52-54] The pattern of growth rate showed a significant decrease beginning 3 years after BMT, the same pattern observed for older prepubertal children receiving TBI.[55] Exogenous growth hormone resulted in improved height outcome for patients treated before puberty. Although most long-term survivors developed sequelae of irradiation, survival performance did not appear to be impaired in the majority of these patients. These patients attend school and participate in activities with a normal level of function. Thus, devastating long-term complications should not be viewed as the natural consequence of TBI as therapy for infant AML.

Several studies have established that MDS can be cured with allogeneic BMT.[4,56-58] Age has been shown to be an important factor, such that patients less than 20 years of age are reported to achieve a DFS of 50% to 65%[4,56]; however, outcome for infants has not been specifically addressed. We demonstrate long-term DFS for 5 of 6 patients, with minimal regimen-related toxicity

or long-term sequelae observed in the current study. These findings are encouraging, because young children with MDS tend to have aggressive disease with early transformation to leukemia, poor response to chemotherapy, and poor long-term survival without marrow transplantation.[59,60] Although numbers are small, our preliminary results suggest that transplantation with alternative donors should be considered for patients without genotypically identical donors, because marrow from matched related, mismatched related, and unrelated donors was used with apparently equal success. Results from a larger series of MDS patients demonstrate superior outcome for children transplanted before leukemic transformation (<25% marrow blasts; unpublished data); thus, our current approach is proceeding to BMT as soon as a suitable donor is identified.

The current study demonstrates that results of marrow transplantation for infants with AML are similar to those for older patients. We show that outcome for infants is primarily determined by relapse as opposed to transplant-related complications. Because infants have a low risk of regimen-related mortality, we recommend proceeding with allogeneic BMT for very young patients with MDS or AML in first remission. Alternative donor grafts appear to be well tolerated by infants and should be sought to permit BMT in the early phase of the disease. To improve DFS for infants transplanted after first remission, efforts should be directed toward reducing the risk of relapse, including the use of intensified preparative regimens or strategies to increase GVL effects. Second transplants may also be required to achieve long-term survival. Long-term sequelae for patients transplanted as infants are not substantially different from those observed in children transplanted at an older age and thus should not be considered a reason to defer BMT.

ACKNOWLEDGMENT

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