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ORIGINAL REPORT

Unrelated Donor Bone Marrow Transplantation for Children With Acute Myeloid Leukemia Beyond First Remission or Refractory to Chemotherapy

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ABSTRACT

Purpose

Identify prognostic factors that influence outcome after unrelated donor bone marrow transplantation in children with acute myeloid leukemia (AML).

Patients and Methods

Included are 268 patients (age ≤ 18 years) with AML in second complete remission (n = 142), relapse (n = 90), or primary induction failure (n = 36) at transplantation. All patients received bone marrow grafts from an unrelated donor and a myeloablative conditioning regimen. Cox regression models were constructed to identify risk factors that influence outcome after transplantation.

Results

In this analysis, the only risk factor that predicted leukemia recurrence and overall and leukemia-free survival was disease status at transplantation. The 5-year probabilities of leukemia-free survival were 45%, 20%, and 12% for patients who underwent transplantation at second complete remission, relapse, and primary induction failure, respectively. As expected, risk of acute but not chronic graft-versus-host disease (GVHD) was lower with T-cell–depleted bone marrow grafts; T-cell–depleted grafts were not associated with higher risks of leukemia recurrence. We observed similar risks of leukemia relapse in patients with and without acute and chronic GVHD.

Conclusion

Children who underwent transplantation in remission had a superior outcome compared with children who underwent transplantation during relapse or persistent disease. Nevertheless, 20% of children who underwent transplantation in relapse are long-term survivors, suggesting that unrelated donor bone marrow transplantation is an effective therapy in a significant proportion of children with recurrent or primary refractory AML.

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INTRODUCTION

Eighty to ninety percent of children with acute myeloid leukemia (AML) treated on current chemotherapeutic trials achieve a complete remission.[1-6] However, 30% to 40% of patients achieving a first remission experience relapse, and less than a third of these patients with recurrent leukemia survive long term.[7-12] Although most reports identify the length of first remission as the best predictor of survival, others have reported that sex and French-American-British classification are predictors of achieving a second remission and long-term survival.[7-12] Therapies for patients who experience relapse are variable and often include allogeneic hematopoietic stem-cell transplantation when a suitable donor is available. In this report, we sought to identify prognostic factors that influence outcome after unrelated donor bone marrow transplantation in children with AML who experience leukemia recurrence after achieving a first complete remission or who received transplantation for primary induction failure.

PATIENTS AND METHODS

Data Collection

The National Marrow Donor Program (NMDP) collects detailed demographic, disease, and transplantation characteristics and outcome data on all unrelated donor transplantations it facilitates in the United States. All patients are observed longitudinally, and computerized error checks, physician review of submitted data, and on-site audits of participating centers ensure data quality. The NMDP retrospectively obtained consent for data submission and study participation from surviving patients or their parent/legal guardian for transplantations it facilitated in the United States before 2002. Thereafter, informed consent was obtained prospectively. The Institutional Review Board of the NMDP waived consent for patients who had died before soliciting consent (transplantations facilitated before 2002). To overcome the bias caused by the inclusion of a proportion of surviving patients (those consenting) but all deceased recipients, and hence their over-representation, a sample of deceased patients was selected using a weighted randomized scheme that adjusts for over-representation of deceased patients in the consented cohort.[13] This weighted randomized scheme was developed based on all survivors in the NMDP database. A logistic regression model was fit to identify the factors that predicted whether a patient had consented or not consented to use of data collected by the NMDP. This analysis found that the following factors were associated with the likelihood of a patient consenting: age, disease type, race, sex, cytomegalovirus serostatus, and country of transplantation (United States *v* not United States). Using estimated consenting probabilities from this model based on the characteristics of dead patients, the biased coin method of randomization was performed to determine which of the dead patients likely would have consented to participate had they been alive. Thus, this procedure includes the dead patients at the same probability as surviving patients who consented to participate. Approximately 13% of surviving patients declined to consent, and 12% of dead patients were deleted by the weighted randomized method. This method was tested several times, and on every occasion, the proportion of deleted dead patients was similar.

Inclusion Criteria

The study population includes 268 recipients of unrelated donor bone marrow transplantations performed in the United States between 1990 and 2003. Patients (age ≤ 18 years at transplantation) with AML who underwent transplantation in second complete remission or first or subsequent relapse and patients with primary induction failure are included. Complete remission was defined as neutrophil count more than 1.0×10^9/L; platelets more than 100×10^9/L; RBC transfusion independent; less than 5% blasts in bone marrow with absence of cells with Auer rods; normal maturation of the erythrocytic, granulocytic, and megakaryocytic series; and absence of extramedullary disease. All patients received bone marrow grafts and a myeloablative transplantation conditioning regimen. Patients who received an unrelated donor bone marrow transplantation in first complete remission, patients in third or subsequent remission, children with Down's syndrome, and recipients of peripheral-blood or umbilical cord blood grafts were excluded because risk factors were likely to vary in these groups.

End Points

The primary outcomes studied were neutrophil and platelet recovery, acute and chronic graft-versus-host disease (GVHD), and early and overall mortality. Neutrophil recovery was defined as achieving an absolute neutrophil count of $\geq 0.5 \times 10^9$/L and platelets more than 20×10^9/L unsupported for 7 days. Failure to achieve an absolute neutrophil count of $\geq 0.5 \times 10^9$/L or a decline to less than 0.5×10^9/L after an initial recovery and without a subsequent recovery was considered graft failure. Incidence of grades 2, 3, and 4 acute GVHD and chronic GVHD were determined in all patients. Diagnosis of acute[14] and chronic GVHD[15] was based on local institutional criteria, with overall grade of acute GVHD assigned retrospectively by the NMDP based on stage of involvement reported for each individual organ. Any death occurring during continuous remission was defined as treatment-related mortality. Relapse was defined as morphologic leukemia recurrence at any site, and leukemia-free survival was defined as survival in a state of continuous complete remission.

Statistical Analysis

The probabilities of leukemia-free and overall survival were calculated using the Kaplan-Meier method.[16] For analysis of survival, death from any cause was considered an event, and data on patients still alive were censored at date of last follow-up. For analysis of leukemia-free survival, leukemia relapse or death from any cause is considered an event, and patients were censored at last follow-up. The probabilities of neutrophil and platelet recovery, acute and chronic GVHD, transplantation-related mortality, and relapse were calculated with the use of the cumulative incidence function method.[16] For neutrophil and platelet recovery and GVHD, death without the event (hematopoietic recovery or GVHD) was the competing event. Data on patients without an event were censored at last follow-up. For relapse, transplantation-related mortality was the competing event, and for transplantation-related mortality, relapse was the competing event. CIs were calculated using log transformation.

Cox regression models were built for analysis of risk factors for GVHD, transplantation-related mortality, relapse, treatment failure, and overall mortality.[17] Multivariate models were built with the use of stepwise forward selection, with $P \leq .01$ considered to indicate statistical significance. The variable for cytogenetic risk group did not attain the level of significance. Given the reported prognostic significance of cytogenetics in AML, analyses for transplantation-related mortality, relapse, treatment failure, and overall mortality were stratified by cytogenetic risk group. All variables met the proportional hazards assumptions. Variables considered in multivariate model building are listed in Table 1. We tested for an effect of transplantation center on outcome and found none.[18] *P* values are two sided. Analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient, disease, and transplantation characteristics by disease status at transplantation are listed in Table 1. Median age at transplantation was 10 years (range, < 1 to 18 years), and median time from diagnosis to transplantation was 13 months (range, < 1 to 88 months). Twenty patients (7%) had myelodysplastic syndrome that evolved to AML before transplantation. Fifty-three percent of patients were in second complete remission, 34% were in first or subsequent relapse at transplantation, and 13% had primary induction failure. Sixty-eight (76%) of 90 patients who underwent transplantation in relapse received chemotherapy before transplantation but did not achieve clinical remission. Most patients (87%) received total-body irradiation–containing conditioning regimens. All patients received bone marrow grafts, and 38% of bone marrow grafts were T-cell depleted. Median follow-up time of surviving patients is 5 years (range, 5 to 156 months).

Hematopoietic Recovery

Most patients achieved neutrophil and platelet recovery. The probability of neutrophil recovery at day 28 was 95% (95% CI, 83% to 98%), and the probability of platelet recovery at day 28 was 70% (95% CI, 64% to 76%).

GVHD

Grade 2 to 4 acute GVHD rates were lower after transplantation of T-cell–depleted bone marrow grafts (hazard ratio [HR] = 0.55; 95% CI, 0.37 to 0.82; $P = .003$); the probability of grade 2 to 4 acute GVHD at day 100 was 31% (95% CI, 22% to 40%) after transplantation of T-cell–depleted bone marrow compared with 52% (95% CI, 44% to 59%) after transplantation of non–T-cell–depleted grafts. In the current analysis, none of the factors tested was predictive for chronic GVHD. The 5-year probability of chronic GVHD was 34% (95% CI, 28% to 40%).

Transplantation-Related Mortality

Transplant-related mortality rates were higher in older patients (age 11 to 18 years) compared with those aged ≤ 10 years. The probabilities of early (day 100) and late (5-year) transplantation-related mortality in patients aged ≤ 10 years were 14% (95% CI, 9% to 21%) and 19% (95% CI, 12% to 26%), respectively; the corresponding probabilities in older patients were 25% (95% CI, 18% to 32%) and 41% (95% CI, 33% to 50%), respectively.

Table 1. Patient, Disease, and Transplantation Characteristics by Disease Status at Transplantation

	Disease Status at Transplantation					
	Second Complete Remission (n = 142)		First or Second Relapse* (n = 90)		Primary Induction Failure (n = 36)	
Characteristic	No. of Patients	%	No. of Patients	%	No. of Patients	%
Male sex	74	52	49	54	17	42
WBC count at diagnosis						
≤ 50 × 10^9/L	75	53	54	60	24	67
> 50-100 × 10^9/L	26	18	11	12	3	8
> 100 × 10^9/L	17	12	11	12	8	22
Unknown	24	17	14	16	1	3
FAB subtype						
M0	1	< 1	—	—	—	—
M1	10	7	15	17	3	8
M2	32	23	24	27	5	14
M3	23	16	2	2	—	—
M4	27	19	14	16	8	22
M5	26	18	6	7	7	19
M6	2	1	3	3	2	6
M7	5	4	11	12	4	11
Unknown	16	10	15	17	7	19
Extramedullary disease at diagnosis						
Absent	115	81	83	92	31	86
CNS ± other sites	20	14	4	4	2	6
Other sites, not CNS	7	5	3	3	3	8
Cytogenetics†						
Good risk	31	22	13	14	2	6
Intermediate risk	72	51	47	52	16	44
Poor risk	10	7	6	7	10	28
Unknown	29	20	24	27	8	22
Age at transplantation, years‡						
≤ 5	50	35	27	30	17	47
> 5-10	19	13	13	14	8	22
> 10-15	41	29	28	31	6	17
> 15-18	32	23	22	24	5	14
Performance score						
90-100	110	77	59	66	24	67
< 90	27	19	28	31	11	31
Unknown	5	4	3	3	1	3
Duration of first complete remission						
≤ 12 months	96	68	75	83	36	100
> 12 months	46	32	28	31	—	—
Unknown	—	—	1	1	—	—
Conditioning regimen						
Irradiation containing	123	86	79	88	32	89
Non–irradiation containing	19	14	11	12	4	11
GVHD prophylaxis						
T-cell depletion	50	35	37	41	14	39
Cyclosporine + methotrexate	70	49	44	49	19	53
Cyclosporine ± other	6	4	2	2	2	6
Tacrolimus ± other	14	10	7	8	1	3
Methotrexate ± other	2	1	—	—	—	—
Donor-recipient sex match						
Male to male	47	33	31	34	10	28
Male to female	34	24	16	18	12	33
Female to male	27	19	18	20	7	19
Female to female	34	24	25	28	7	19
Donor-recipient CMV serostatus						
Donor negative/recipient negative	54	38	37	41	16	44
Donor positive/recipient negative	25	18	16	18	5	14
Donor negative/recipient positive	29	20	18	20	6	17
Donor positive/recipient positive	31	22	15	17	8	22
Unknown	3	2	4	4	1	3

(continued on following page)

Table 1. Patient, Disease, and Transplantation Characteristics by Disease Status at Transplantation (continued)

Characteristic	Second Complete Remission (n = 142) No. of Patients	%	First or Second Relapse* (n = 90) No. of Patients	%	Primary Induction Failure (n = 36) No. of Patients	%
Donor age, years						
18-30	42	30	22	24	9	25
31-40	58	41	35	39	11	31
41-50	35	25	26	29	12	33
51-60	7	5	7	8	4	11
Donor-recipient HLA disparity						
Matched§	42	30	22	24	13	36
One locus mismatched‖	61	43	43	48	12	33
> One locus mismatched¶	39	27	25	28	11	31

Abbreviations: FAB, French-American-British; GVHD, graft-versus-host disease; CMV, cytomegalovirus.
*Sixty-six patients were in first relapse, 24 patients were in second relapse, and three patients were aplastic at transplantation.
†Cytogenetic classification (Medical Research Council of the United Kingdom) was as follows: good risk: inv16/t(16;16)/del(16q), t(15;17), t(8;21) ± secondary abnormalities; intermediate risk: normal, 11q23 abn, +8, del(9q), del(7q), +21, +22, all others; and poor risk: del(5q)/−5, −7, abn(3q), t(9;22), t(6;9), complex karyotypes (≥ five unrelated abnormalities).
‡Nine patients were ≤ 1 year old at transplantation.
§Matched: 66 patients were matched at HLA-A, HLA-B, HLA-C, and DRB1 (allele level); three were matched at HLA-A, HLA-B, and DRB1 (allele level) and HLA-C (low resolution); seven were matched at HLA-A, HLA-B, HLA-C (low resolution), and DRB1; and one was matched at HLA-A, HLA-B, and DRB1 (allele level, HLA-C typing not known).
‖One locus mismatched: 48 patients were mismatched at one locus considering allele-level typing at HLA-A, HLA-B, HLA-C, and DRB1; 13 were mismatched at one locus considering low-resolution typing at HLA-A, HLA-B, and HLA-C and matched at DRB1; 55 were matched (low resolution) at HLA-A and HLA-B and mismatched at one locus at DRB1, with data on HLA-C not known.
¶> One locus mismatched: 46 patients were mismatched at more than one locus considering allele-level typing at HLA-A, HLA-B, HLA-C, and DRB1; 25 were mismatched at one locus considering HLA-A, HLA-B, and DRB1, with HLA-C not known; four were mismatched at one locus considering low-resolution typing at HLA-A, HLA-B, and DRB1, with HLA-C not known.

Relapse

Relapse rates were higher in patients who underwent transplantation in first or second relapse and at primary induction failure compared with patients who underwent transplantation in second complete remission, stratified for cytogenetic risk (Table 2). Rates were similar when transplantation was performed at relapse or primary induction failure (HR = 1.33; 95% CI, 0.73 to 2.40; P = .355). The 5-year probabilities of leukemia recurrence were 22% (95% CI, 15% to 29%), 57% (95% CI, 46% to 67%), and 51% (95% CI, 34% to 66%) for patients who underwent transplantation in second complete remission, relapse, and primary induction failure, respectively (Fig 1). The duration of first complete remission was not associated with

Table 2. Multivariate Analysis of Transplantation Outcome: Treatment-Related Mortality, Leukemia Relapse, Treatment Failure (relapse or death, inverse of leukemia-free survival), and Overall Mortality Stratified by Cytogenetic Risk Group

Outcome and Disease Status at Transplantation	No. of Patients	Total No. of Patients Assessable	Hazard Ratio	95% CI	*P*
Transplantation-related mortality					
≤ 10 years old at transplantation	24	134	1.00		
> 10-18 years old at transplantation	55	134	2.20	1.35 to 3.60	.002
Relapse					
Second complete remission	29	142	1.00		< .001*
Primary induction failure	18	36	4.33	2.28 to 8.19	< .0001
First or subsequent relapse	51	90	3.41	2.15 to 5.40	< .0001
Treatment failure					
Second complete remission	75	142	1.00		< .001*
Primary induction failure	31	36	2.59	1.64 to 4.09	< .001
First or subsequent relapse	71	90	1.77	1.27 to 2.45	.001
Overall mortality					
Second complete remission	72	142	1.00		.004*
Primary induction failure	29	36	2.10	1.32 to 3.34	.002
First or subsequent relapse	62	90	1.46	1.03 to 2.06	.032

NOTE. The variable for cytogenetic risk group was nonproportional in the model for overall mortality; therefore, multivariate models for treatment-related mortality, relapse, treatment failure, and overall mortality were stratified by cytogenetic risk group. The following categories were collapsed because there were no differences between groups: disease status at transplantation: first relapse and second relapse; and age at transplantation: ≤ 5 and > 5-10 years and > 10-15 and > 15-18 years.
*Two *df* test.

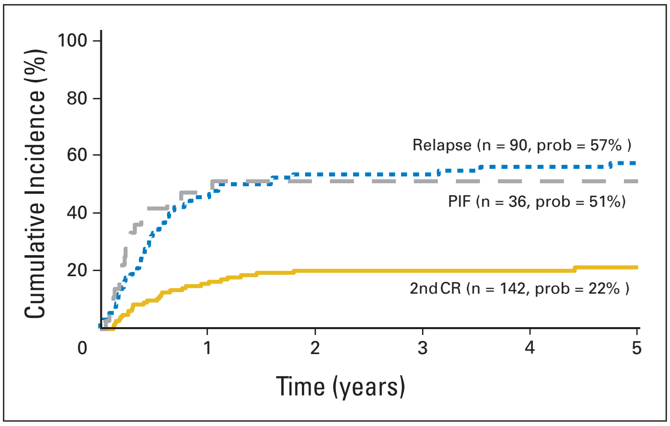

Fig 1. The 5-year probabilities of leukemia relapse after unrelated donor bone marrow transplantation by disease status at transplantation. PIF, primary induction failure; CR, complete remission.

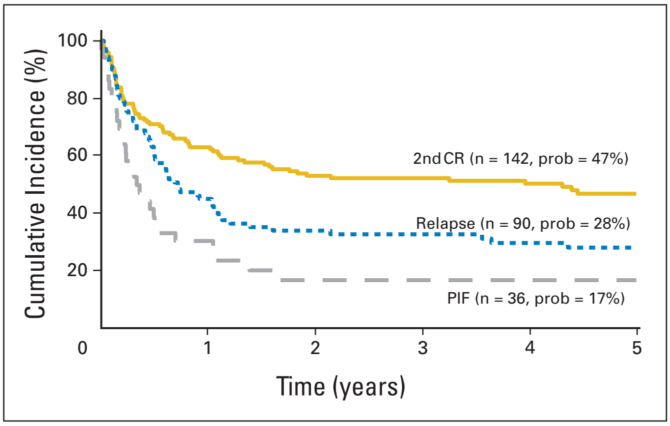

Fig 2. The 5-year probabilities of overall survival after unrelated donor bone marrow transplantation by disease status at transplantation. PIF, primary induction failure; CR, complete remission.

leukemia recurrence after transplantation (HR = 1.61; 95% CI, 0.91 to 2.86; *P* = .106). In the current study, we observed similar rates of relapse in patients with and without acute and chronic GVHD (data not shown).

Leukemia-Free Survival

Treatment failure rates (relapse or death; inverse of leukemia-free survival) were higher in patients who underwent transplantation in first or second relapse and primary induction failure, stratified for cytogenetic risk (Table 2). Failure rates were similar when transplantation was performed in primary induction failure and in relapse (HR = 1.56; 95% CI, 0.98 to 2.48; *P* = .059). Treatment failure rates were not associated with duration of first complete remission (HR = 1.43; 95% CI, 0.95 to 2.13; *P* = .084). The 5-year probabilities of leukemia-free survival were 45% (95% CI, 37% to 54%), 20% (95% CI, 13% to 30%), and 12% (95% CI, 3% to 26%) for patients who underwent transplantation in second clinical remission, relapse, and primary induction failure, respectively.

Overall Survival

One hundred sixty-three patients died; overall mortality rates were higher in patients who underwent transplantation in primary induction failure compared with patients who underwent transplantation in second complete remission, stratified for cytogenetic risk (Table 2). The 5-year probabilities of overall survival were 47% (95% CI, 38% to 55%), 28% (95% CI, 19% to 38%), and 17% (95% CI, 7% to 32%) for patients who underwent transplantation in second complete remission, relapse, and primary induction failure, respectively (Fig 2). Mortality rates were similar in patients who underwent transplantation in primary induction failure compared with patients in relapse (HR = 1.48; 95% CI, 0.91 to 2.39; *P* = .111). Recurrent leukemia was the cause of death in 85 of 163 patients who died. Other causes of mortality included GVHD (n = 18), infection (n = 30), adult respiratory distress syndrome or interstitial pneumonitis (n = 9), hemorrhage (n = 8), organ failure (n = 11), and graft failure (n = 2).

DISCUSSION

Sibling donor transplantation in first remission has been used for many years as a primary approach to treatment of AML, with survival rates of 60% to 70% reported from many centers and cooperative groups.[2,3,5,6] Improvements in risk stratification on the basis of genetic abnormalities in leukemic blasts and more effective chemotherapy protocols now allow the identification of subgroups of children with AML for whom transplantation is deemed unnecessary in first remission because cure with chemotherapy is equally likely.[2] In parallel with interest in limiting use of transplantation in children with a good prognosis, there is increased interest in investigating whether unrelated donor transplantation can improve outcomes for children with particularly poor prognoses, such as those with primary induction failure and those who relapse after a first remission.[11,19,20] In this study, we have explored outcomes in a large group of children receiving unrelated donor transplantations facilitated by the NMDP in the United States to determine how successful this therapy is in rescuing children for whom chemotherapy has been ineffective and to identify risk factors that predict a good outcome after transplantation.

The majority of children included in this study underwent transplantation in second remission. Overall, outcomes were encouraging, with almost half of the children receiving transplantation in second complete remission surviving 5 years later and significant numbers of survivors among the children with refractory disease receiving transplantation. In the current report, the only risk factor that predicted relapse, overall survival, and leukemia-free survival was disease status at the time of transplantation, with children who underwent transplantation in second complete remission having superior outcomes to children who underwent transplantation in relapse or with primary refractory disease. Despite this, 28% of children who underwent transplantation in relapse and 17% of children who underwent transplantation with primary induction failure were alive 5 years after transplantation, suggesting that transplantation can cure at least some children with the most resistant disease. It is perhaps surprising that length of first complete remission did not predict outcome in our study. This may be a reflection of the demographics of the patients, the majority of whom had experienced relapse early, with first complete remission of less than 12 months, limiting statistical power to look at this risk factor.

Children receiving transplantation in remission clearly had a superior outcome to those who underwent transplantation in relapse. It is commonly debated whether it is preferable to perform transplantation in children identified in early relapse immediately or to pursue reinduction chemotherapy and attempt to achieve a second remission before performing transplantation. Although our data show better disease control in children who underwent transplantation in remission, these patients had chemotherapy-sensitive disease and would, therefore, be expected to have better outcomes. Importantly, 76% of the patients who underwent transplantation in relapse had received chemotherapy but did not achieve remission; however, these patients had a 5-year probability of overall survival of 28%. This result suggests that transplantation is worthwhile in this group of particularly difficult patients. Our data are unable to definitively answer the question of the efficacy of immediate transplantation without an attempt at reinduction because there were only 22 such patients in this study. However, the 5-year leukemia-free survival rate was 25% in this group, which is similar to the rate in the group for whom reinduction was attempted. Most of the 22 patients reported good performance scores (90 to 100) despite a high tumor burden; nine patients had peripheral blasts, 10 patients had marrow blast counts of more than 10%, and three patients had marrow blast counts of 5% to 10%. We did not observe differences in leukemia-free survival rates after transplantation for patients in first relapse and second relapse, but there were only 24 patients in the latter group, and our inability to observe differences may be explained by the relatively small number of patients (5-year leukemia-free survival rates of 19% and 22%, respectively).

The importance of adverse cytogenetics was challenging to assess in this group. Our analysis failed to show a significant effect of intermediate- or poor-risk cytogenetics on leukemia recurrence, leukemia-free survival, or overall survival. This may be explained by the fact that patients with recurrent leukemia have high-risk disease, and consequently, the relevance of cytogenetics is limited by the relatively small sample size of approximately 260 patients. Data on cytogenetics were not available for approximately 23% of patients, which is a limitation that occurs when using data reported to an observational database and when transplantations are performed over a 10-year period because cytogenetic testing was not routinely performed during the early years. We adjusted for this limitation by stratifying all analysis of risk factors for transplantation outcome by cytogenetic risk group given the prognostic importance of cytogenetics for this disease.

Almost one third of grafts in this study were T-cell depleted. Although T-cell depletion reduced acute GVHD rates, treatment-related mortality was unchanged, as were leukemia-free and overall survival and relapse, indicating a neutral effect of T-cell depletion on overall outcome. As reported by others, we did not observe lower chronic GVHD rates after T-cell–depleted transplantations.[21] Age and WBC count at diagnosis were not associated with transplantation outcome after a first relapse. This is similar to observations by Webb et al[11] on outcome for children with relapsed AML after treatment on the Medical Research Council AML 10 trial at diagnosis. We did not observe a graft-versus-leukemia effect in our cohort. This may be explained by the inclusion of patients who received T-cell–depleted grafts (38% of patients) and patients with high tumor burden (47% of patients underwent transplantation in relapse or primary induction failure).

This study represents the largest series of children receiving unrelated donor bone marrow transplantation for AML currently in the literature. The strengths of the study are its large size and high-quality audited data. The limitations of the study are its retrospective nature, the heterogeneity inevitable in registry studies describing aggregate outcomes of transplantations performed at multiple centers, and our inability to compare transplantation outcomes to those after chemotherapy alone in a similar group of patients. We did not observe a significant correlation between year of transplantation, HLA mismatch, and survival, and this may be explained by the relatively few patients who received allele-matched bone marrow grafts in this report. Larger studies in unrelated donor bone marrow transplantation clearly demonstrate the negative effect of HLA mismatch on survival, and matching between donor and recipient using allele-level typing at HLA-A, HLA-B, HLA-C, and DRB1 represents the current standard of care.[22] Despite these limitations, these data indicate that unrelated donor bone marrow transplantation is an effective therapy for a significant proportion of children with recurrent or refractory AML who are unlikely to be cured with chemotherapy alone.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

