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ORIGINAL REPORT

Hematopoietic Stem-Cell Transplantation for Acute Leukemia in Relapse or Primary Induction Failure

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ABSTRACT

Purpose
Patients with acute leukemia refractory to induction or reinduction chemotherapy have poor prognoses if they do not undergo hematopoietic stem-cell transplantation (HSCT). However, HSCT when a patient is not in complete remission (CR) is of uncertain benefit. We hypothesized that pretransplantation variables may define subgroups that have a better prognosis.

Patients and Methods
Overall, 2,255 patients who underwent transplantation for acute leukemia in relapse or with primary induction failure after myeloablative conditioning regimen between 1995 and 2004 were reported to the Center for International Blood and Marrow Transplant Research. The median follow-up of survivors was 61 months. We performed multivariate analysis of pretransplantation variables and developed a predictive scoring system for survival.

Results
The 3-year overall survival (OS) rates were 19% for acute myeloid leukemia (AML) and 16% for acute lymphoblastic leukemia (ALL). For AML, five adverse pretransplantation variables significantly influenced survival: first CR duration less than 6 months, circulating blasts, donor other than HLA-identical sibling, Karnofsky or Lansky score less than 90, and poor-risk cytogenetics. For ALL, survival was worse with the following: first refractory or second or greater relapse, ≥ 25% marrow blasts, cytomegalovirus-seropositive donor, and age of 10 years or older. Patients with AML who had a predictive score of 0 had 42% OS at 3 years, whereas OS was 6% for a score ≥ 3. Patients with ALL who had a score of 0 or 1 had 46% 3-year OS but only 10% OS rate for a score ≥ 3.

Conclusion
Pretransplantation variables delineate subgroups with different outcomes. HSCT during relapse can achieve long-term survival in selected patients with acute leukemia.

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INTRODUCTION

Patients with acute leukemia refractory to initial or reinduction chemotherapy have dismal prognoses if they do not undergo hematopoietic stem-cell transplantation (HSCT). The utility of transplantation for patients not in complete remission (CR), however, is controversial. Since 1990, 12 studies have reported series with more than 30 patients who underwent transplantation while not in CR,[1-12] which included 39 to 230 (median, 63) patients per report. Disease-free survival (DFS) ranged from 2% to 32%. Selection bias for the healthiest patients and publication bias with more frequent reports for favorable series confound interpretation of these data. Eligibility criteria between series were variable, which precluded a meaningful comparison. The last study from the Center for International Blood and Marrow Transplant Research (CIBMTR) of refractory acute leukemia examined 126 patients who underwent transplantation from 1982 to 1989.[1] Thus, the outcome of patients transplanted in the past 20 years without CR is largely unknown.

The prognostic factors for these transplantations in relapse are also controversial. Several factors have been associated with better outcome, though not consistently, and they include the following: absence of blasts in blood,[1,4,6,9,10] fewer marrow blasts (ie, 5% or 30%),[1,6,10,12] primary induction failure,[8] untreated first relapse,[2] cytogenetics,[11] matched unrelated donor,[4,8] matched sibling donor,[5] female donor,[7] female recipient,[1] younger

donor,[4] younger recipient,[1,2,7] better pretransplantation performance score,[1,9] absence of significant infection at transplantation,[1] middle-range tacrolimus levels,[9] and presence of acute[2,3,7] or chronic[7] graft-versus-host disease (GVHD). In better-risk groups defined by these criteria, DFS ranged from 28% to 50%. However, these studies reported heterogeneous populations and generally included too few patients to perform a multivariate analysis of relevant pretransplantation risk factors.

To facilitate patient counseling and clinical decision making and to define the role of HSCT in patients without CR, we analyzed outcomes of 2,255 patients who underwent transplantation during relapse or primary induction failure reported to the CIBMTR from 1995 to 2004, and we developed a predictive scoring system for survival.

PATIENTS AND METHODS

Data Sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), the Autologous Blood and Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program (NMDP) established in 2004, which collects data from more than 450 transplantation centers worldwide. The Statistical Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis collects, verifies, and audits data and performs observational analyses in compliance with the privacy rule (ie, Health Insurance Portability and Accountability Act) as a Public Health Authority after review and approval by the institutional review boards of the National Marrow Donor Program and the Medical College of Wisconsin. CIBMTR data includes Transplant Essential Data plus more detailed comprehensive disease and pre- and post-transplantation clinical information from a subset of patients selected by a weighted randomization scheme. Data are collected pretransplantation, 100 days post-transplantation, 6 months post-transplantation, and annually thereafter or until death.

Patients

The outcomes of 2,255 patients with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) who underwent a first myeloablative allogeneic bone marrow (BM) or peripheral-blood (PB) HSCT in relapse or primary induction failure between 1995 and 2004 are reported. Patients with AML and preceding myelodysplastic syndrome (MDS; n = 343) and patients with secondary leukemia were included, but those with chronic myeloid leukemia in blast crisis were not. Only patients who received total-body irradiation (TBI) or busulfan-based myeloablative conditioning regimens were analyzed. Patients receiving reduced-intensity or fludarabine-containing conditioning regimen (n = 488) were excluded. Patients undergoing syngeneic transplantations (n = 14) or cord-blood transplantations (n = 164) also were excluded.

Before analysis, we stratified disease status at HSCT into four categories. Primary induction failure was reported by the transplantation team. First untreated relapse was defined as first relapse without chemotherapy between relapse and the pre-HSCT conditioning regimen. First refractory relapse was defined as first relapse with chemotherapy (but no CR) between relapse and HSCT. Other patients were categorized as second and later relapse.

Patients with ALL were classified as having poor-risk cytogenetics with either t(4:11), t(9;22), t(8;14), hypodiploidy or near triploidy, or more than five cytogenetic abnormalities.[13] Other ALL cytogenetic findings were classified as other abnormalities or normal. Patients with AML were classified according to the Eastern Cooperative Oncology Group/Southwest Oncology Group classification as good risk (inv16, t[8;21], t[15;17]), poor risk (−5/del[5q], −7/del[7q], inv[3q], abn11q, 20q or 21q, del[9q], t[6;9], t[9;22], abn17p, and complex karyotype defined as three or more abnormalities), or intermediate (other and normal karyotypes).[14]

Study End Points

The primary study end point was 3-year overall survival (OS). OS was defined as time from the date of transplantation to the date of death or last contact. For HSCT during relapse, because post-HSCT CR was not always achieved or reliably documented, it was therefore not possible to calculate the incidence of relapse, transplantation-related mortality, or disease-free survival (DFS). Neutrophil and platelet engraftment were defined as the first of 3 consecutive days with an absolute neutrophil count greater than 0.5×10^9/L or untransfused platelet count greater than 20×10^9/L. Acute GVHD (aGVHD) was defined by consensus criteria,[15] whereas chronic GVHD (cGVHD) was classified according to the standard criteria in use before the recent National Institutes of Health consensus conference report.[16]

HLA typing methods and resolution varied over the period of study. Donor-recipient pairs, therefore, were reclassified as well matched, partially matched, or mismatched according to recently published CIBMTR criteria.[17] Well-matched pairs had either no identified HLA mismatch and informative data at the four loci (ie, HLA-A, -B, and -C, and DRB1) or allele matching at the four loci. Partially matched pairs had a defined, single locus mismatch and/or or single locus that was missing HLA data. Mismatched pairs had two or more allele or antigen mismatches.

Statistical Analysis

Probability of 3-year OS was calculated by using the Kaplan-Meier estimator. Confidence intervals were calculated with a log transformation. Multivariate analyses were performed separately for AML and ALL. The probability of neutrophil and platelet recovery, and of aGVHD and cGVHD, were calculated by using cumulative incidence method to accommodate competing risks.

The effect of pretransplantation variables on OS at 3 years was compared by using a pseudovalue regression model.[18] This technique reduces to a logistic regression model when there is no censoring and accounts for censored observations before 3 years. By using a log-log link function, this can be thought of as a pointwise Cox proportional hazards model that incorporates pretransplantation variables of interest. Factors that influenced outcomes were identified by stepwise forward selection multivariate model. Any covariate with a P value $< .05$ was considered significant. The following variables were considered in multivariate analyses: age at transplantation, donor and recipient sex, Karnofsky or Lansky performance score at HSCT, disease status at HSCT, circulating blasts, less than 25% marrow blasts at HSCT, time from relapse to transplantation, duration of first CR for patients in first relapse, pre-HSCT extramedullary leukemia, prior MDS, cytogenetics, prior fungal infection, conditioning regimen, donor-recipient sex and sex match, donor-recipient HLA match, donor-recipient cytomegalovirus (CMV) status, graft type, GVHD prophylaxis, and year of transplantation. Analyses were performed by using SAS software, version 9.1 (SAS Institute, Cary, NC).

Because multivariate analysis showed that some pretransplantation variables were associated with outcome, a scoring system was developed to link the significant pretransplantation risk factors with outcome. Several scoring models were tested and were based on placement of patients with similar risks in the same category on the basis of the fitted model. The scoring models were evaluated by using a Brier score approach, a function that is based on the calculation of the average squared deviation between predicted probabilities and outcomes.[19] The scoring model that gave the lowest Brier score was picked as the best model.

RESULTS

Patients Characteristics

The 2,255 patients included 1,673 with AML from 221 centers in 34 countries and 582 with ALL from 180 centers in 33 countries. The

Table 1. Patient, Disease, and Transplantation Characteristics

Characteristic	Patients by Disease					
	AML			ALL		
	No. Evaluable	No. (n = 1,673)	%	No. Evaluable	No. (n = 582)	%
No. of centers		221			180	
Age, years						
Median		38			29	
Range		< 1-70			< 1-60	
Male sex		880	53		371	64
Karnofsky or Lansky score < 90 at transplantation	1,595	759	48	553	262	47
WBC at diagnosis, $\times 10^9$/L	1,443			484		
Median		11			21	
Range		< 1-1,803			< 1-990	
< 50		1,079	75		329	68
≥ 50		364	25		155	32
Prior history of extramedullary leukemia		233	14		192	33
Prior history of CNS disease	862	80	9	394	104	26
Prior history of myelodysplasia		343	21		NA	
Marrow blasts at transplantation, %	1,428			488		
Median		21			17	
Range		0-100			0-100	
< 25		753	53		277	57
≥ 25		675	47		211	43
Blasts in blood at transplantation, $\times 10^9$/L	1,524			518		
Median		4.2			0	
Range		0-12,798			0-24,116	
0		656	43		320	62
≥ 0		868	57		198	38
Cytogenetics for AML						
Good		117	7			
Intermediate/normal		988	59			
Poor		273	16			
Unknown		295	18			
Cytogenetics for ALL						
High risk					151	26
Other					138	24
No abnormalities					145	25
Unknown					148	25
Disease status at transplantation						
Primary induction failure		636	38		144	25
First untreated relapse		322	19		67	12
First refractory relapse		428	26		251	43
First relapse, unknown treatment		9	1		9	2
Second or additional relapse		278	17		111	19
Time from relapse to transplantation for HSCT in first refractory relapse, months						
Median		2.5			3.0	
Range		< 1-23			< 1-16	
< 3		257	60		127	51
≥ 3		171	40		124	49
Duration of first CR for patients in relapse, months	1,566			501		
Median		5			8	
Range		< 1-113			< 1-97	
< 6		515	55		140	39
≥ 6		415	45		217	61
Prior fungal infection		250	15		70	12
Conditioning regimen						
CyTBI + other		456	27		241	41
CyTBI		489	29		167	29
BuCy + other		285	17		59	10
BuCy		320	19		40	7
Bu or TBI ± other		123	7		75	13

(continued on following page)

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

Characteristic	Patients by Disease					
	AML			ALL		
	No. Evaluable	No. (n = 1,673)	%	No. Evaluable	No. (n = 582)	%
Donor-recipient sex						
M-M		549	33		227	39
M-F		440	26		117	20
F-M		331	20		144	25
F-F		353	21		94	16
Donor-recipient CMV serostatus	1,615			564		
−/−		447	28		151	27
+/−		223	14		76	13
−/+		426	26		145	26
+/+		519	32		192	34
Donor-recipient HLA match						
HLA-identical sibling		552	33		224	38
Other related		117	7		49	8
Well-matched unrelated		354	21		116	20
Partially matched unrelated		419	25		126	22
Mismatched unrelated		231	14		67	12
Graft type						
Bone marrow		1,095	65		376	65
PBSC		578	35		206	35
Year of transplantation						
1995-1996		429	26		163	28
1997-1998		382	23		122	21
1999-2000		292	17		105	18
2001-2002		288	17		106	18
2003-2004		282	17		86	15
GVHD prophylaxis						
T-cell depletion		213	13		51	9
(Tacrolimus or CsA) + MTX ± other		1,198	72		436	75
(Tacrolimus or CsA) ± other		224	13		80	14
Other		38	2		15	3

NOTE. First refractory relapse is defined as transplantation in first relapse with chemotherapy between relapse and conditioning.

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; NA, not applicable; HSCT, hematopoietic stem-cell transplantation; CR, complete remission; Cy, cyclophosphamide; TBI, total-body irradiation; Bu, busulfan; CMV, cytomegalovirus; PBST, peripheral-blood stem cells; GVHD, graft-versus-host disease; CsA, cyclosporine; MTX, methotrexate.

median follow-up of survivors was 61 months in both disease groups (range, 2 to 137 months).

Patient, disease, and HSCT characteristics are listed in Table 1. The median age was 38 years for patients with AML and was 29 years for patients with ALL. Nearly half had a pre-HSCT Karnofsky score less than 90. Only 15% and 12% in the AML and ALL groups, respectively, had pre-HSCT fungal infections. More than 40% had greater than 25% marrow blasts at HSCT, whereas 57% of patients with AML and 38% of patients with ALL had circulating blasts. For the patients who underwent transplantation in first or later relapse, the duration of the first CR was less than 6 months in 55% of patients with AML and in 39% of patients with ALL.

At HSCT, 38% of patients with AML and 25% of patients with ALL were in primary induction failure, whereas 45% of patients with AML and 55% of patients with ALL were in first relapse; 19% and 12% of these patients with AML and ALL, respectively, in first relapse were in first untreated relapse. For those who underwent transplantation in first refractory relapse, the median times between relapse and HSCT were 2.5 and 3 months for patients with AML and ALL, respectively. Transplantations in second or later relapse were infrequent (17% and 19% in patients with AML and ALL, respectively).

Transplantation Characteristics

Cyclophosphamide plus TBI was included in pre-HSCT conditioning for 56% of patients with AML and for 70% of patients with ALL, whereas 36% of patients with AML and 17% of the patients with ALL received busulfan plus cyclophosphamide. Just greater than one third of patients received matched sibling donor grafts, and two thirds of all grafts were marrow. GVHD prophylaxis included methotrexate and a calcineurin inhibitor for 85% of patients with AML and 89% of patients with ALL. Ex vivo T-cell depletion was uncommon (13% of patients with AML and 9% of patients with ALL).

Engraftment and GVHD

As listed in Table 2, 90% had neutrophil and 66% had platelet recovery by day 100. Grades 3 to 4 aGVHD occurred in 23% of patients with AML and in 27% of patients with ALL. cGVHD occurred in 27% of the patients, nearly all within the first year after HSCT.

Survival and Cause of Death

OS rates at 3 years were 19% for patients with AML (95% CI, 17% to 21%) and 16% for patients with ALL (95% CI, 13% to 20%). The mortality rate at 100 days after transplantation was 39% in AML, and

Table 2. Univariate Probabilities of Outcome Among Patients Who Underwent Transplantation With Acute Leukemia in Relapse or Primary Induction Failure

Variable	Univariate Probabilities of Outcome by Disease					
	AML			ALL		
	No. of Patients Evaluable	Probability	95% CI*	No. of Patients Evaluable	Probability	95% CI*
ANC $> 0.5 \times 10^9$/L	1,660			579		
At 100 days		90	87 to 92		89	83 to 93
Platelets $> 20 \times 10^9$/L	1,627			561		
At100 days		66	63 to 69		66	61 to 69
Acute GVHD, grades 2-4	1,653			570		
At 100 days		48	45 to 51		52	47 to 56
Acute GVHD, grades 3-4	1,652			572		
At 100 days		23	21 to 26		27	24 to 31
Chronic GVHD	1,649			568		
At 1 years		25	23 to 28		26	22 to 30
At 3 years		27	25 to 29		27	23 to 32
At 5 years		27	25 to 30		27	23 to 32
Overall survival	1,673			582		
At 6 months		44	42 to 46		42	38 to 46
At 1 year		29	27 to 31		28	24 to 32
At 3 years		19	17 to 21		16	13 to 20
At 5 years		17	15 to 19		14	11 to 17
Overall mortality	1,673			582		
At 100 days		39	36 to 41		41	37 to 45

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; GVHD, graft-versus-host disease.
*Kaplan-Meier or cumulative incidence, as appropriate.

it was 41% in ALL. As listed in Table 3, leukemia was the main cause of death and occurred at rates of 42% of AML and 37% of ALL. Other causes of death were similarly frequent in patients with ALL and AML.

Multivariate Analysis and Prognostic Scoring System

Multivariate analysis for OS at 3 years in AML is summarized in Table 4. Compared with HSCT after primary induction failure, survival after HSCT in first relapse was worse after short (ie, $<$ 6 months) initial CR and better after longer (ie, $>$ 6 months) initial CR. For patients who underwent transplantation in first relapse, survival was similar for refractory or untreated relapse. For patients with AML, survival was worse for patients with circulating blasts, a mismatched unrelated donor, a related donor other than an HLA-matched sibling, a Karnofsky or Lansky score less than 90, and poor-risk cytogenetics. By using these five risk factors (ie, first CR duration $<$ 6 months, circulating blasts, non–HLA-identical sibling donor, performance score $<$ 90%, poor-risk cytogenetics), a prognostic scoring system was established (Table 5). Patients with a score of 0 (n = 148) had a 42% 3-year OS (95% CI, 34% to 50%), whereas patients with a score $\geq$ 3 (n = 321) had only 6% 3-year OS (95% CI, 3% to 9%; Fig 1).

Multivariate analysis for patients with ALL (Table 4) demonstrated superior survival for HSCT in primary induction failure or first untreated relapse, with fewer than 25% marrow blasts, with a CMV-seronegative donor, and with age younger than 10 years. By using these four risk factors (ie, refractory first or later relapse, $\geq$ 25% marrow blasts, CMV-positive donor, age $>$ 10 years), a prognostic scoring system also was established for patients with ALL (Table 5). Patients with a score of 0 or 1 (n = 47) had 46% survival at 3 years (95% CI, 32% to 61%), whereas patients with a score $\geq$ 3 (n = 301) had only 10% 3-year OS (95% CI, 6% to 13%; Fig 1).

Table 3. Causes of Death Among Patients Who Underwent Transplantation With Acute Leukemia in Relapse or Primary Induction Failure

Cause of Death	Patients by Disease					
	AML			ALL		
	No. Evaluable (n = 1,673)	No.	%	No. Evaluable (n = 582)	No.	%
Overall No. of deaths	1,370			491		
Leukemia relapse or progression		641	42		208	37
Graft failure		12	1		6	1
Infection		232	15		72	13
Graft-versus-host disease		111	7		45	8
Organ failure		180	12		88	16
Hemorrhage		43	3		15	3
Idiopathic pneumonia/ ARDS		120	8		48	9
Secondary malignancy		9	1		3	1
Other/unknown		22	1		6	1

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ARDS, acute respiratory distress syndrome.

DISCUSSION

This study demonstrated that HSCT can induce long-term survival in patients with acute leukemia who are not in CR: 19% with AML and 16% with ALL were alive at 3 years after transplantation. Outcome varied according to pretransplantation variables, and this allowed for

Table 4. Multivariate Analysis for 3-Year Survival

Variable by Disease	No. of Patients	Death Outcome		
		Relative Risk	95% CI	P^*
AML				
Disease status at transplantation				$P_{overall} < .001$
Primary induction failure	636	1.00		
Duration of first CR ≤ 6 months	514	1.26	1.06 to 1.51	.01†
Duration of first CR > 6 months	414	0.83	0.69 to 0.99	.0401
Duration of first CR unknown	100	0.92	0.68 to 1.24	.5987
Blasts in blood at transplantation				$P_{overall} < .001$
Absent	749	1.00		
Present	673	1.48	1.28 to 1.72	.0000
Missing/negative	242	1.27	0.98 to 1.64	.0753
Donor-recipient HLA match				$P_{overall} < .001$
HLA-identical sibling	544	1.00		
Other related	117	2.21	1.51 to 3.23	.0000*
Well-matched unrelated	354	1.25	1.02 to 1.54	.0279
Partially matched unrelated	419	1.15	0.96 to 1.38	.1426
Mismatched unrelated	230	1.46	1.15 to 1.84	.0017
Karnofsky or Lansky score				$P_{overall} < .001$
< 90	754	1.00		
90-100	832	0.65	0.56 to 0.76	.0000
Missing	78	0.58	0.42 to 0.81	.0012
Cytogenetics*				$P_{overall} = .0226$
Good	117			
Intermediate	981	1.13	0.86 to 1.50	.3791
Poor	272	1.47	1.06 to 2.04	.0225
Unknown	294	1.37	1.00 to 1.89	.0528
ALL				
Disease status at transplantation				$P_{overall} = .0003$
Primary induction failure	144	1.00‡		
First untreated relapse	67	1.34	0.83 to 2.15	.2312
First refractory relapse	251	2.10	1.43 to 3.09	.0002
Second and additinoal relapse	111	2.58	1.53 to 4.34	.0004
Blasts in marrow at transplantation, %				$P_{overall} = .0014$
< 25	277	1.00‡		
≥ 25	211	1.75	1.18 to 2.58	.0053
Missing	94	2.21	1.34 to 3.66	.0020
Donor/recipient CMV status				$P_{overall} = .0058$
−/−	151	1.00‡		
+/−	76	1.66	0.99 to 2.80	.0555
−/+	145	1.06	0.73 to 1.53	.7718
+/+	192	2.28	1.43 to 3.63	.0005
Missing	18	0.95	0.43 to 2.10	.9039
Age, years				$P_{overall} < .001$
< 1-9	55	1.00‡		
10-19	102	1.76	1.03 to 3.02	.0403
20-29	146	1.75	1.06 to 2.91	.0296
30-39	127	1.57	0.95 to 2.60	.0769
40-49	105	4.75	2.37 to 9.53	<.001
50-59	46	1.46	0.79 to 2.70	.2309

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; ALL, acute lymphoblastic leukemia; CMV, cytomegalovirus.
*P shown overall and as pairwise comparisons with reference group.
†Pairwise comparison: duration of first CR < 6 months v > 6 months ($P < .001$).
‡Reference group.

the development of a predictive scoring system. Higher-risk patients had a 3-year survival of only 6% in AML and 10% in ALL, whereas 3-year survival for lower-risk patients was 42% in AML and 46% in ALL.

The absence of post-transplantation remission in some patients confounded the calculation of relapse rate, transplantation-related mortality, and DFS; thus, we used 3-year OS as the primary end point. In this setting, post-transplantation survival estimates can be used for clinical decision making and patient counseling. Use of 3-year survival as a proxy for DFS is additionally validated by the minimal decrease in survival between 3 and 5 years after transplantation—only 2% in each group. For these patients with advanced disease, leukemia was the

Table 5. Scoring System for Post-HSCT Outcome in AML and ALL

Outcome by Disease	Score	No. of Patients
AML		
Disease group		
PIF or duration of first CR > 6 months	0	763
Duration of first CR < 6 months	1	374
Cytogenetics prior to HSCT		
Good or intermediate	0	901
Poor	1	236
HLA match group		
HLA identical sibling or well matched or partially matched unrelated	0	900
Mismatched unrelated	1	156
Related other than HLA identical sibling	2	81
Circulating blasts		
Absent	0	503
Present	1	634
Karnofsky or Lansky score		
90-100	0	604
< 90	1	533
ALL		
Disease group		
PIF or first untreated relapse	0	172
First refractory relapse	1	206
Second and additional relapse	2	92
Donor CMV		
Negative	0	235
Positive	1	235
Bone marrow blasts, %		
< 25	0	268
> 25	1	202
Age, years		
1-9	0	45
10-39	1	302
> 40	2	123

NOTE. Overall score is defined as the sum of the scores for each risk factor. For AML, four risk groups were defined as follows: score of 0, 1, 2, and ≥ 3. For ALL, three risks groups were defined as follows: score of 0 or 1; 2; and ≥ 3.

Abbreviations: HSCT, hematopoietic stem-cell transplantation; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; PIF, primary induction failure; CR, complete remission; CMV, cytomegalovirus.

most common single cause of all deaths—42% for AML and 37% for ALL—whereas 58% of AML and 63% of ALL deaths were attributable to nonrelapse causes.

Transplantation for patients with acute leukemia who are not in CR has been controversial.[1-12] Nevertheless, 306 of the 371 CIBMTR allotransplant centers reported such patients, which represented 34% and 20% of the patients who underwent transplantation for AML and ALL, respectively, between 1995 and 2004. The OS rates of 16% and 19% in AML and ALL, respectively, are low but offer some hope when interpreted by using critical prognostic factors. Indeed, disease burden at HSCT was often considerable: 40% of the patients had more than 25% marrow blasts and more than half had circulating blasts. Performance score was also low, as nearly half had a Karnofsky or Lansky score less than 90.

To guide the choice whether to proceed to transplantation, we developed a predictive scoring system by using the significant and easily measured pretransplantation variables associated with outcome in a multivariate analysis. Patients with a score ≥ 3 have a dismal outcome, and alternative therapy or other HSCT approaches should be considered. Conversely, we suggest strong consideration of HSCT for patients with a risk score ≤ 2, because their predicted 3-year survival is between 15% and 46%.

Our multivariate analysis may also aid other transplantation-related decision making. The type of myeloablative conditioning regimen, TBI in the conditioning, GVHD prophylaxis, and graft source (ie, PB or bone marrow) did not affect outcome. Therefore, our data do not suggest critical importance for these variables in decision making. There was no impact of the donor type in ALL, whereas all closely matched donors yielded comparable survival in AML. These data suggest that, in the absence of an HLA-identical sibling, a well-matched or partially matched unrelated donor can result in satisfactory outcome. Robust data of umbilical cord blood for HSCT in this population are unavailable.

These data can also influence the choice between immediate transplantation or additional chemotherapy aimed at transplantation in CR. Patients who underwent transplantation with primary induction failure had the best prognosis, which suggests that HSCT should be considered early in patients resistant to initial induction chemotherapy. Indeed, additional chemotherapy could result in toxicity that might limit the success of transplantation. In patients with ALL in first relapse, the prognosis was better in untreated early relapse, which suggests that transplantation should be considered before reinduction chemotherapy. However, our data may reflect a selection of even more aggressive disease for patients still not achieving CR after reinduction chemotherapy. Thus, these data do not enable us to reliably compare transplantation in first relapse versus chemotherapy aimed towards transplantation in second CR.

This retrospective study did not include cord-blood transplantations or reduced-intensity conditioning regimens. Two studies of cord-blood transplantation reported small numbers of patients without CR with outcomes similar to those observed in this study.[20,21] A retrospective analysis showed that nonmyeloablative and myeloablative regimens had the same outcome in advanced AML and MDS.[22] Three studies of reduced-intensity regimens in patients with relapsed or refractory disease reported rates of OS of 15%, 32%, and 45%, although inherent clinical selection of which advanced leukemia patients should receive reduced-intensity allografts seriously confound interpretation of these outcome data.[23-25] We could not examine the impact of intensity and length of immunosuppression or the occurrence and severity of GVHD. Most importantly, this predictive model needs to be interpreted cautiously, as it has not been studied prospectively or confirmed with an independent validation cohort. Despite these limitations, our study provides powerful data to guide clinical decision making about HSCT for acute leukemia during relapse.

These data showed that the survival rates of lower-risk patients are almost comparable to those of series of patients who underwent transplantation in CR. However, they also highlight the need for improved treatment strategies for the higher-risk patients. The single most frequent cause of failure was leukemia progression. Additional research on newer antileukemic agents is thus needed to bring patients to CR before transplantation or to incorporate these pharmacologic or immunotherapeutic approaches into the peritransplantation therapy for patients with advanced acute leukemia.

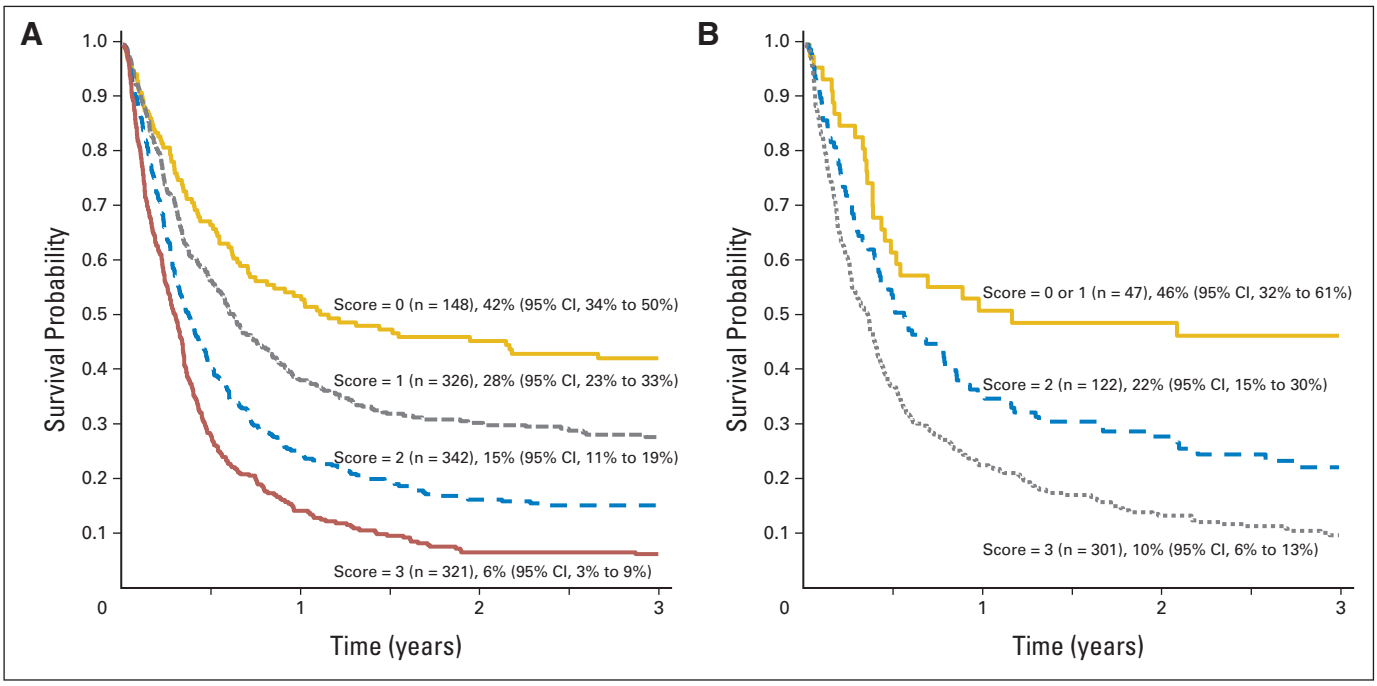

Fig 1. Probability of overall survival after transplantation with acute leukemia in relapse or primary induction failure according to risk score (ie, [A] acute myeloid leukemia score of 0, 1, 2, and ≥ 3; [B] acute lymphoblastic leukemia score of 0 and 1; 2; and ≥ 3).The 3-year survival rates and 95% CIs are indicated.

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