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ORIGINAL REPORT

Nonmyeloablative Allogeneic Hematopoietic Cell Transplantation in Patients With Acute Myeloid Leukemia

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ABSTRACT

Purpose
Allogeneic hematopoietic cell transplantation (HCT) after high-dose conditioning regimens imposes prohibitively high risks of morbidity and mortality for patients with high-risk acute myeloid leukemia (AML) who are older or have comorbid conditions. Here, we examined outcomes after nonmyeloablative allogeneic HCT in such patients.

Patients and Methods
Two hundred seventy-four patients (median age, 60 years) with de novo or secondary AML underwent allogeneic HCT from related (n = 118) or unrelated donors (n = 156) after conditioning with 2 Gy of total-body irradiation (TBI) with or without fludarabine. A calcineurin inhibitor and mycophenolate mofetil were used for postgrafting immunosuppression.

Results
With a median follow-up of 38 months in surviving patients, the estimated overall survival at 5 years was 33%. The estimated 5-year relapse/progression and nonrelapse mortality rates were 42% and 26%, respectively. The cumulative incidences of grades 2, 3, and 4 acute graft-versus-host disease (GVHD) were 38%, 9%, and 5%, respectively. The cumulative incidence of chronic GVHD at 5 years was 44%. Patients in first and second complete remission had better survival rates than patients with more advanced disease (37% and 34% *v* 18%, respectively). Patients with HLA-matched related or unrelated donors had similar survivals. Unfavorable cytogenetic risk status was associated with increased relapse and subsequent mortality. Chronic GVHD was associated with lower relapse risk.

Conclusion
Allogeneic HCT from related or unrelated donors after conditioning with low-dose TBI and fludarabine, relying almost exclusively on graft-versus-leukemia effects, can result in long-term remissions in older or medically infirm patients with AML.

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INTRODUCTION

According to Surveillance, Epidemiology, and End Result statistics, the median patient age at the diagnosis of acute myeloid leukemia (AML) is 67 years. The treatment of older patients with AML remains challenging. Approximately 55% to 80% of adults with de novo AML achieve complete remissions when treated with induction therapy.[1,2] These remissions, however, are rarely durable; multiple cycles of high-dose cytarabine have become the standard consolidation for patients with favorable/intermediate cytogenetic risk younger than age 60 years.[3] Patients older than age 60 years or those with comorbid conditions are usually treated with less intense regimens because of their inability to tolerate multiple cycles of high-dose chemotherapy, although a recent study by Lowenberg et al[4] reported encouraging results with escalated doses of daunorubicin. In this group of patients, long-term leukemia-free survival rates are typically 10% to 15%.[5,6] Similarly, although allogeneic hematopoietic cell transplantation (HCT) after myeloablative conditioning represents a postremission therapy option with curative potential for younger patients,[7,8] concerns about treatment-related morbidity and mortality have limited its use in older patients and in those with pre-existing medical conditions.[9]

In recent years, the development of reduced-intensity conditioning regimens has enabled older and medically infirm patients to undergo allogeneic

HCT. These approaches rely more heavily on potent graft-versus-leukemia (GVL) effects for tumor eradication. A number of studies of reduced-intensity conditioning followed by allogeneic HCT for the treatment of AML have been published,[10-22] with long-term (2- to 4-year) survival rates ranging between 28% and 54%. Here, we report a multicenter experience with allogeneic HCT after nonmyeloablative conditioning with low-dose (2 Gy) total-body irradiation (TBI) with or without fludarabine in patients with AML.

PATIENTS AND METHODS

Eligibility

This analysis included all patients with de novo or secondary AML who received nonmyeloablative conditioning on multi-institutional protocols between March 4, 1998 and September 30, 2008 (Table 1). Patients were treated at 17 centers (Appendix Table A1, online only). The Fred Hutchinson Cancer Research Center (FHCRC; Seattle, WA) acted as coordinating center. Protocols and consents were approved by institutional review boards of the FHCRC and collaborating centers. All patients signed informed consent forms approved by local institutional review boards.

Patients with related or unrelated donors were eligible for nonmyeloablative conditioning if they were older than 55 or 50 years, respectively. Younger patients were included if they had otherwise prohibitive comorbid conditions. Patients in first complete remission (CR1) were only eligible if they had unfavorable cytogenetic abnormalities, had secondary AML, and/or were older than 60 years. Patients in subsequent remissions or with primary refractory leukemia were also eligible. Exclusion criteria were left ventricular ejection fraction less than 40%, pulmonary carbon monoxide diffusion capacity less than 35% of predicted value, severe liver dysfunction, or serologic evidence of HIV infection.

Pretransplantation Characteristics

Complete remission (CR) was defined according to standard morphologic criteria[23]; morphologic CR with incomplete blood count recovery (absolute neutrophil count $< 1{,}000/\mu L$ and/or platelet count $< 100{,}000/\mu L$) was included. Cytogenetic risk was stratified per Southwest Oncology Group criteria.[24] Minimal residual disease (MRD) was assessed by multiparameter flow cytometry, karyotype analysis, and fluorescence in situ hybridization when applicable, performed within 30 days before HCT. Pretransplantation comorbidities were assessed using the HCT comorbidity index (HCT-CI).[25]

HLA Typing and Matching

Patients and donors were tested for HLA-A, -B, and -C by at least intermediate-resolution DNA typing and HLA-DRB1 and -DQB1 by high-resolution techniques.[26]

Conditioning Regimen and Postgrafting Immunosuppression

Patients were conditioned with a single fraction of 2 Gy TBI at a rate of 0.07 to 0.20 Gy/min from linear accelerators or opposing dual cobalt-60 sources on day 0, with or without fludarabine at 30 $mg/m^2/d$ on days -4 through -2 before HCT. Postgrafting immunosuppression consisted of cyclosporine or tacrolimus combined with mycophenolate mofetil.[27-30]

Post-HCT Monitoring

Patients underwent marrow aspirations on days 28, 84, 180, and 360 after HCT to assess for AML. Donor chimerism was evaluated in peripheral-blood T cells, granulocytes, and marrow cells on days 28, 84, 180, and 360 after HCT as described.[31] Acute and chronic graft-versus-host disease (GVHD) were graded as described.[32,33] Toxicities occurring within the first 100 days were scored using Common Terminology Criteria for Adverse Events version 3.0.

Causes of Death

In patients whose AML relapsed or progressed, relapse/progression was listed as cause of death regardless of other events. In patients with GVHD on immunosuppressive therapy who died from infections, GVHD was listed as cause of death. Infection was listed as cause of death when occurring without

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients (N = 274)	%
Age, years		
Median	60	
Range	5-74	
AML type		
De novo	188	69
Secondary	86	31
AML stage		
CR1	160	58
MRD present	29	
CR2	71	26
MRD present	13	
CR > 2	28	10
MRD present	11	
Relapse/refractory*	15	6
Cytogenetic risk		
Favorable	14	5
Intermediate	117	43
Unfavorable	85	31
Unknown prognostic significance	48	18
Data not available	10	4
Time from diagnosis to HCT, months		
Median	8.8	
Range	2.2-226.7	
< 6	77	28
6-18	134	49
≥ 18	63	23
No. of high-dose chemotherapy cycles		
All patients		
Median	3	
Range	1-16	
Patients in CR1		
Median	3	
Range	1-6	
Donor		
HLA identical (related)	117	43
HLA matched (unrelated)	123	45
HLA mismatched	34	12
Related	1	
Unrelated	33	
Conditioning		
TBI, 2 Gy	28	10
FLU, TBI 2 Gy	246	90
Stem-cell source		
Marrow	5	2
PBSC	269	98
Median $CD34^+$ cell dose, $\times 10^6/kg$	6.9	
Median $CD3^+$ cell dose, $\times 10^8/kg$	2.9	
GVHD prophylaxis†		
MMF, CSP	194	71
Tacrolimus	80	29
Follow-up, months		
Median	38	
Range	6-122	
Durable engraftment		95

Abbreviations: AML, acute myeloid leukemia; CR1, first complete remission; MRD, minimal residual disease; CR2, second complete remission; CR, complete remission; HCT, hematopoietic cell transplantation; TBI, total-body irradiation; FLU, fludarabine; PBSC, peripheral-blood stem cells; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; CSP, cyclosporine A.

*The median marrow blast count among 15 patients in relapse was 11% (range, 7% to 60%); three of these patients had circulating blasts, and one had CNS relapse.

†CSP or tacrolimus was administered orally twice daily starting on day −3. MMF was started on day 0 and was given to all patients twice daily initially; subsequently, the protocols were altered so that recipients of unrelated-donor allografts received MMF three times daily to reduce the risks of graft rejection and acute GVHD.

relapse/progression or GVHD. All deaths without relapse/progression were considered nonrelapse mortality (NRM).

Statistical Analysis

Data were analyzed as of April 22, 2009. Overall survival (OS) was estimated using the Kaplan-Meier method. Cumulative incidence estimates were calculated using methods previously described. Death was treated as a competing risk in the analyses of relapse/progression and acute and chronic GVHD. Relapse/progression was treated as a competing risk when analyzing NRM. Cox regression was used for univariate and multivariate analyses of risk factors for all time-to-event end points; all *P* values were two-sided and derived from likelihood ratio statistics.

RESULTS

Patient Characteristics

Results on 63 (23%) of 274 patients[34] have been previously reported. Median age was 60 years (range, 5 to 74 years). One hundred eighty-eight patients had de novo AML, and 86 had secondary AML, which was therapy related in 23 patients and evolved from myelodysplastic syndrome or myeloproliferative disorder in 63 patients. Of the 274 patients, 160 were in CR1, 71 were in second CR (CR2), and 43 had more advanced leukemia. Among 264 patients with cytogenetic data available, 14 had favorable risk (three patients in CR1), 117 had intermediate risk, and 85 had unfavorable cytogenetics, whereas 48 patients had cytogenetic aberrations of unknown prognostic significance. Fifty-three patients in morphologic CR had minimal residual disease at HCT, of whom 33 (62%) had unfavorable cytogenetics. Among patients in morphologic CR, 53 had evidence of minimal residual disease, and 197 did not; data were not available in nine patients. Median time from diagnosis to HCT was 8.8 months (range, 2.2 to 226.7 months).

Transplantation Details

One hundred seventeen patients had HLA-identical sibling donors, and 123 patients had HLA-matched unrelated donors. Thirty-four donors were HLA mismatched at the antigen or allele level, 33 of whom were unrelated.

Twenty-eight patients received 2-Gy TBI alone, and 246 patients received 2-Gy TBI and fludarabine as additional immunosuppression. Two hundred sixty-nine patients received granulocyte colony-stimulating factor–mobilized peripheral-blood mononuclear cell grafts, whereas five patients received unrelated marrow grafts. Median $CD34^+$ and $CD3^+$ cell doses were 6.9×10^6/kg and 2.9×10^8/kg recipient weight, respectively.

Engraftment

The median neutrophil nadir occurred 15 days after HCT and was 200 cells/μL (range, 0 to 2,000 cells/μL). The median duration of neutrophil counts less than 500 cells/μL was 10 days (range, 1 to 100 days). The median platelet nadir occurred 9 days after HCT and was 30,000/μL; the median duration of platelet counts less than 20,000/μL was 4 days (range, 1 to 46 days).

Four patients died before day +28. Of the remaining 270 patients, 258 (96%) had sustained engraftment. Median day +28 peripheral-blood T-cell and granulocyte donor chimerism levels (available in 260 and 187 patients, respectively) were 77.5% and 99%, respectively. Corresponding levels on day +84 were 85% and 100%, respectively. Engrafting patients received grafts containing a median of 2.9×10^8/kg and 7.0×10^6/kg $CD3^+$ and $CD34^+$ cells, respectively.

Twelve patients (4%) experienced graft rejection, which was primary in six patients (never $>$ 5% donor T cells) and secondary in six patients (declines in donor T cells to $\leq$ 5% after initial engraftment). Two of the 12 patients (both in CR1) received 2-Gy TBI, whereas 10 patients received 2-Gy TBI and fludarabine. In patients with graft rejection, five patients had HLA-identical related grafts, six had HLA-matched unrelated grafts (three patients received marrow), and one had an HLA-A antigen-mismatched unrelated graft. Overall, rejected grafts contained a median of 2.4×10^8/kg $CD3^+$ cells and 4.0×10^6/kg $CD34^+$ cells. In the six patients with primary graft rejection, median $CD3^+$ and $CD34^+$ cell doses were 0.3×10^8/kg and 2.7×10^6/kg, respectively. Although the median $CD34^+$ cell doses were comparable between engrafting and rejecting patients, the $CD3^+$ cell dose was approximately a log lower in patients with primary graft rejection than in patients with durable engraftment or secondary graft rejection.

Five patients who experienced graft rejection underwent second allogeneic HCT, and four of these patients died (relapse, n = 1; NRM, n = 3). Seven patients did not undergo second HCT; one is alive with MDS, and six died of relapse, despite donor lymphocyte infusions in two patients.

GVHD and Toxicity

Acute GVHD developed at a median of 42 days after HCT. The cumulative incidences of grade 2, 3, and 4 acute GVHD were 38%, 9%, and 5%, respectively (Figs 1A and 1B). The cumulative incidence of grade 2 acute GVHD was less with HLA-identical related donors than with HLA-matched unrelated donors (28% *v* 43%, respectively), whereas the incidences of grade 3-4 acute GVHD were comparable (12% each). The rates of both grade 2 and grade 3-4 acute GVHD were higher in patients with HLA-mismatched unrelated grafts (50% and 24%, respectively). Chronic GVHD developed in 43% of patients (Fig 1C), with similar cumulative incidences among all three patient groups (44%, 41%, and 41% in HLA-identical related, HLA-matched unrelated, and HLA-mismatched donors, respectively). Grade 4 nonhematologic toxicities were uncommon and included mainly pulmonary, cardiovascular, and hepatic toxicities (15, 11, and 10 events, respectively).

Relapse, Progression, and Relapse-Related Mortality

The median follow-up time of surviving patients was 38 months (range, 6 to 122 months). Of the 274 patients, 113 developed relapse/progression, which was fatal in 106. The overall 5-year probability of relapse/progression was 42%. Median time to relapse/progression was 84 days. Patients with favorable/intermediate and unclassified cytogenetics had lower 5-year relapse/progression rates than patients with unfavorable cytogenetics (36%, 32%, and 55%, respectively; Fig 2B). The 5-year probabilities of relapse/disease progression for patients in CR1, CR2, and with advanced/refractory AML were 39%, 41%, and 52%, respectively (Figs 3A, 3B, and 3C). Although HLA-mismatched unrelated recipients seemed to have less 5-year relapse/progression than HLA-matched related or unrelated recipients (25% *v* 47% and 42%, respectively), these differences did not reach statistical significance.

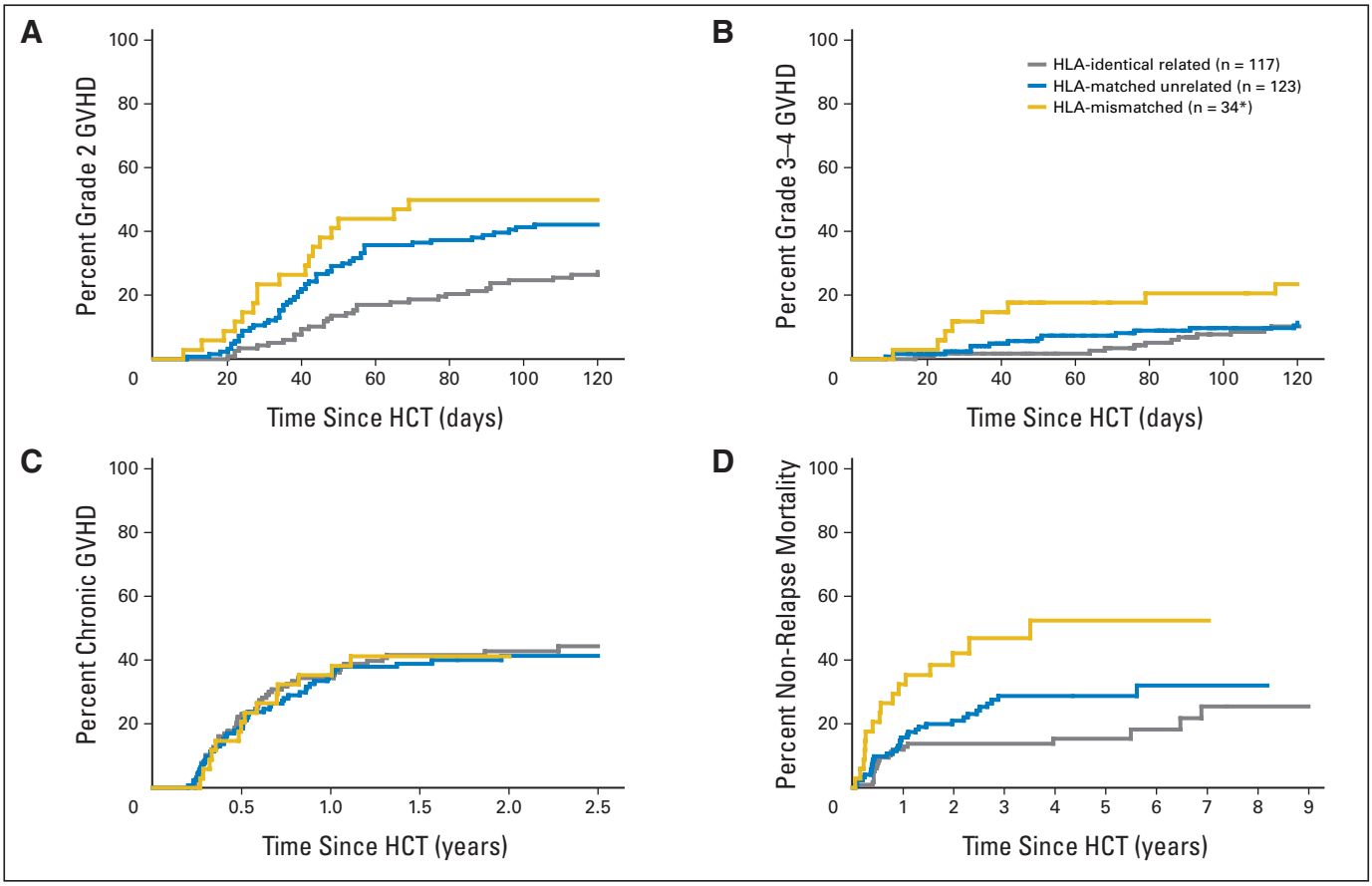

Fig 1. Cumulative incidences of (A) grade 2 acute graft-versus-host disease (GVHD), (B) grade 3 or 4 acute GVHD, and (C) chronic GVHD. (D) Estimated probability of nonrelapse mortality stratified by donor type. (*) Thirty-three of the HLA-mismatched donors were unrelated. HCT, hematopoietic cell transplantation.

Patients with unfavorable cytogenetics, patients with minimal residual disease, patients undergoing HCT within 6 months of diagnosis, and patients with incomplete peripheral-blood cell count recoveries before HCT had higher risks of relapse/progression in univariate analysis (Table 2). Factors without statistically significant impact on relapse/progression were age, AML stage, etiology (de novo *v* secondary), and donor type (HLA-identical related *v* HLA-matched unrelated *v* HLA-mismatched unrelated). In a multivariate model, the impacts of MRD and peripheral-blood cell count recovery lost statistical significance, whereas cytogenetic risk status and time between diagnosis and HCT remained significantly associated with relapse/progression and overall mortality.

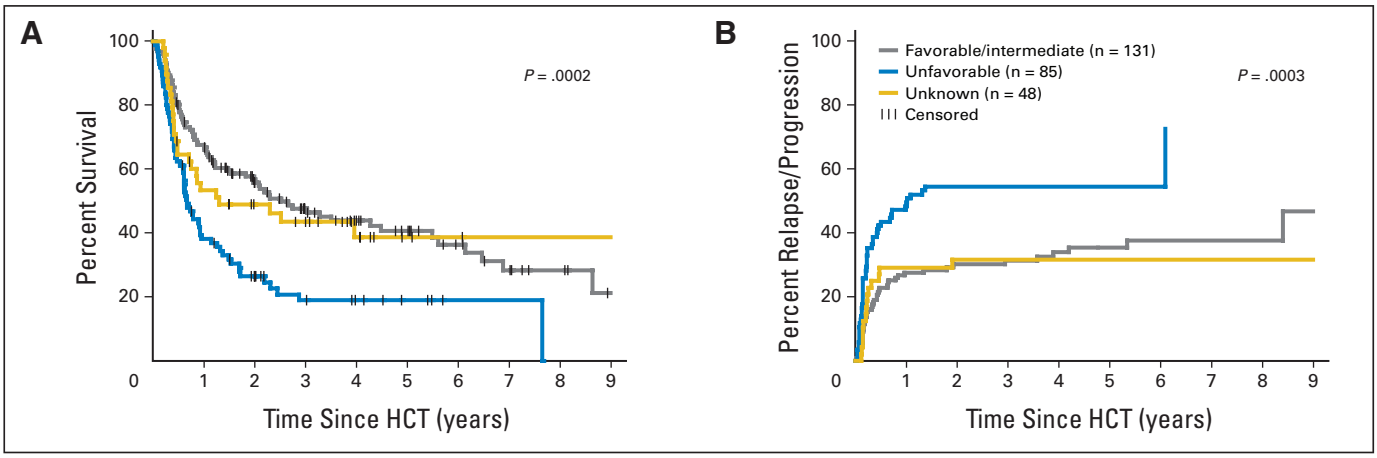

Fig 2. (A) Overall survival and (B) relapse/progression stratified by cytogenetic risk before hematopoietic cell transplantation (HCT). Total number of patients was 264 because cytogenetic data were not available in 10 patients.

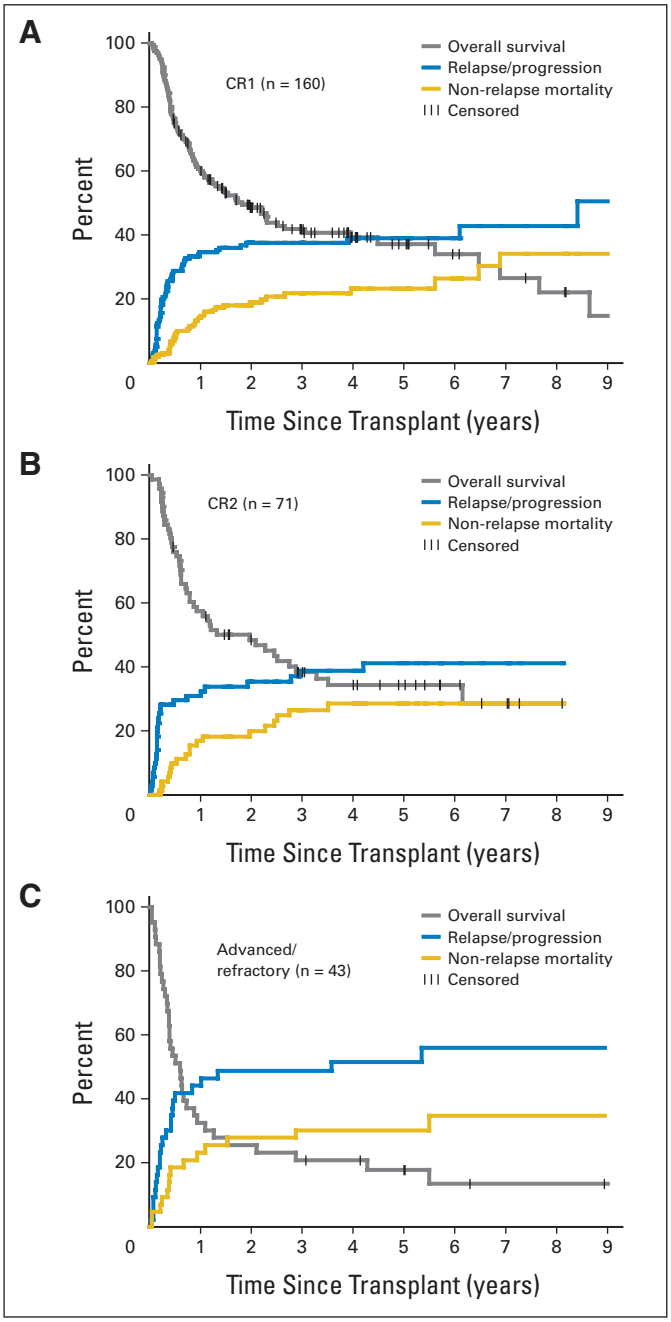

Fig 3. Overall survival, relapse/progression rate, and nonrelapse mortality of patients with acute myeloid leukemia in first complete remission (CR1), in second complete remission (CR2), and with more advanced/refractory disease.

More advanced AML was associated with greater risks of relapse and mortality. The presence of MRD was not identified as an independent risk factor for relapse/progression, possibly because of its close association with unfavorable cytogenetics; 33 (62%) of 53 patients with MRD had unfavorable cytogenetics.

Similarly, among patients in CR1, the absence of pre-HCT peripheral-blood cell count recovery, unfavorable cytogenetics, and MRD were associated with increased risk of relapse/progression in univariate analysis (Table 2; Appendix Figs A1A and A1B, online only); cytogenetics and peripheral-blood cell count recovery remained significantly associated with relapse/progression in a multivariate model. Cytogenetics was the single factor influencing overall mortality in a multivariate model for patients in CR1 (Appendix Table A2, online only).

In a time-dependent analysis, the presence of acute GVHD (grade ≥ 2) did not affect relapse/progression. In contrast, chronic GVHD was associated with a significant decrease in relapse/progression (Table 3).

Survival and Causes of Death

At the time of last follow-up, 99 of 274 patients were alive. The 5-year rates of OS and disease-free survival were 33% and 32%, respectively. Patients in CR1 and CR2 had better 5-year OS than patients with more advanced AML (37% and 34%, respectively, *v* 18%; $P = .008$; Fig 3). Patients with HLA-mismatched unrelated donors had slightly worse 5-year OS than patients with HLA-matched related or unrelated donors, which was not statistically significant (22% *v* 37% and 33%, respectively; $P = .37$). Patients with HLA-identical related donors had lower NRM than patients with HLA-matched or HLA-mismatched unrelated donors (18% *v* 29% and 52%, respectively; $P = .005$; Fig 1D). In addition, patients with favorable/intermediate and unclassified cytogenetics had better OS than patients with unfavorable cytogenetics (41% and 39%, respectively, *v* 19%; $P < .001$; Fig 2A). The leading cause of death was relapse (106 patients).

Risk Factors for NRM

The 100-day, 1-year, and 5-year NRM rates were 4%, 16%, and 26%, respectively. The majority of NRM was caused by GVHD or a combination of GVHD and infections (48 patients; Appendix Table A3, online only). Patients with HLA-matched and HLA-mismatched unrelated donors had increased risk of NRM and mortality in a multivariate analysis (Appendix Table A2). Age at HCT, the etiology of AML, pre-HCT CBC recovery, and HCT-CI scores did not have statistically significant impacts on NRM. Although there was a tendency of increased NRM for patients with HCT-CI scores of ≥ 4, this remained a trend ($P = .08$; Appendix Table A2).

DISCUSSION

Patients with AML older than 60 years of age have a poor prognosis with conventional chemotherapy and are usually not candidates for allogeneic HCT with high-dose conditioning regimens. Allogeneic HCT after a variety of reduced-intensity conditioning regimens has been introduced in recent years, with encouraging results reported in patients with AML.[11-15,17,21] Many studies used fludarabine-based conditioning regimens with addition of an alkylating agent and, in some cases, in vivo T-cell depletion with antithymocyte globulin or alemtuzumab.[10,12-14]

At the FHCRC, a low-dose TBI-based conditioning regimen has been developed based on studies in a canine HCT model.[35-39] The regimen consists of 2-Gy TBI with or without fludarabine[40] and post-grafting immunosuppression with a calcineurin inhibitor and mycophenolate mofetil. The regimen has relied almost entirely on GVL effects for treating AML.

The engraftment rate in this study was 96%. The median donor $CD3^+$ cell dose was almost a log lower in patients with primary graft

Table 2. Risk Factors for Relapse/Progression in Univariate and Multivariate Analyses

Variable	No. of Patients	Univariate Analysis			Multivariate Analysis*		
		HR for Relapse/ Progression	95% CI	*P*	HR for Relapse/ Progression	95% CI	*P*
All patients							
Age at HCT, years							
< 60	139	1.0		.66	1.0		.97
≥ 60	135	0.92	0.6 to 1.3		1.01	0.6 to 1.6	
AML etiology							.84
De novo	188	1.0		.09	1.0		
Secondary	86	1.40	1.0 to 2.1		1.06	0.6 to 1.8	
AML stage							
CR1	160	1.0		.14	1.0		< .001
CR2	71	1.06	0.7 to 1.7		2.51	1.4 to 4.6	
Advanced/refractory	43	1.65	1.0 to 2.7		5.89	3.0 to 12	
MRD at HCT†							
No	197	1.0		.02	1.0		.83
Yes	53	1.76	1.1 to 2.8		1.07	0.6 to 1.9	
Cytogenetic risk							
Favorable/intermediate	131	1.0		< .001	1.0		.001
Unfavorable	85	2.27	1.5 to 3.4		2.71	1.6 to 4.6	
Unknown prognostic significance	48	0.98	0.5 to 1.8		1.18	0.6 to 2.3	
Months from diagnosis to HCT							
< 6	77	1.0		< .001	1.0		< .001
6-18	134	0.88	0.6 to 1.3		0.81	0.5 to 1.4	
≥ 18	63	0.34	0.2 to 0.6		0.15	0.1 to 0.4	
Blood count recovery at HCT							
Yes	141	1.0		.05	1.0		.06
No	112	1.49	1.0 to 2.2		1.55	1.0 to 2.5	
Donor							
HLA-identical sibling	117	1.0		.21	1.0		.39
HLA-matched unrelated donor	134	0.94	0.6 to 1.4		1.03	0.6 to 1.7	
HLA-mismatched unrelated donor	34	0.54	0.3 to 1.1		0.59	0.2 to 1.5	
Patients in CR1							
Age at HCT, years							
< 60	73	1.0		.17	1.0		.42
≥ 60	87	0.71	0.4 to 1.2		0.78	0.4 to 1.4	
AML etiology							
De novo	102	1.0		.26	1.0		.50
Secondary	58	1.34	0.8 to 2.2		0.79	0.4 to 1.6	
MRD at HCT							
No	125	1.0		.02	1.0		.48
Yes	29	2.10	1.2 to 3.8		1.33	0.6 to 2.9	
Cytogenetic risk							
Favorable/intermediate	71	1.0		.002	1.0		.01
Unfavorable	50	2.33	1.3 to 4.1		2.60	1.2 to 5.6	
Unknown prognostic significance	33	0.74	0.3 to 1.6		0.81	0.3 to 2.0	
Months from diagnosis to HCT							
< 6	72	1.0		.07	1.0		.91
≥ 6	88	0.60	0.3 to 1.0		0.96	0.5 to 1.9	
Blood count recovery at HCT							
Yes	91	1.0		.03	1.0		.02
No	55	1.83	1.1 to 3.2		2.24	1.1 to 4.4	
Donor							
HLA-identical sibling	75	1.0		.62	1.0		.35
HLA-matched unrelated donor	69	0.90	0.5 to 1.5		1.19	0.6 to 2.4	
HLA-mismatched unrelated donor	16	0.62	0.2 to 1.8		0.52	0.1 to 2.0	

NOTE. The No. of prior high dose-chemotherapy treatment cycles and HCT Comorbidity Index scores were also included in the model but did not have statistically significant association with the risk of relapse/progression.

Abbreviations: HR, hazard ratio; HCT, hematopoietic cell transplantation; AML, acute myeloid leukemia; CR1, first complete remission; CR2, second complete remission; MRD, minimal residual disease.

*Data on all variables were available for 226 patients undergoing HCT with nonmyeloablative conditioning. In the subgroup of patients in CR1, data on all variables were available for 130 patients.

†Among 250 patients in morphologic complete remission in univariate analysis; among 215 patients in morphologic complete remission in multivariate analysis.

Table 3. Time-Dependent Analysis of Risk Factors for Overall Mortality, Relapse/Progression, and Nonrelapse Mortality

	Overall Mortality			Relapse/Progression			Nonrelapse Mortality		
Factor	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Acute GVHD grade	1.0		< .001	1.0		.22	1.0		< .001
0/1									
3	1.21	0.9 to 1.7		1.11	0.7 to 1.7		1.76	1.0 to 3.2	
3/4	3.38	2.2 to 5.1		0.45	0.1 to 1.4		11.6	6.3 to 21	
Chronic extensive GVHD	1.0		.07	1.0		.01	1.0		.36
No									
Yes	0.71	0.5 to 1.0		0.42	0.2 to 0.8		1.32	0.7 to 2.4	

Abbreviations: HR, hazard ratio; GVHD, graft-versus-host disease.

rejection than in patients with durable engraftment, emphasizing the role T cells play in engraftment. The degree of HLA disparity did not impact the rate of engraftment in this cohort.

Allogeneic HCT after conditioning with 2-Gy TBI with or without fludarabine was well tolerated in this cohort of older and/or medically infirm patients and resulted in improved OS rates in all disease stages. With a median follow-up time of 38 months, patients in CR1 had an estimated 5-year OS rate of 37%, which represents an improvement when compared with historical data using chemotherapy only (reported 3-year survival rates of 2% to 15%[41]), especially when considering that current patients in CR1 were either older than 60 years or had unfavorable cytogenetics and/or secondary AML. The 5-year OS in patients in CR2 and with more advanced AML (34% and 18%, respectively) was also better than expected than with chemotherapy alone (11% at 5 years for 667 patients in first relapse in a study by Breems et al[42]).

Patients in the current study were slightly older compared with patients in other reports of allogeneic HCT after reduced-intensity conditioning, (median age, 60 years *v* 58,[11] 56,[15] 53,[21] and 52 years,[13] respectively); however, the current 5-year NRM rate of 26% was comparable to the rates reported by others, which ranged from 20% to 53% at 2 and 4 years.[10,14,21] The leading cause of NRM in current patients was GVHD, resulting in death in 18% of patients; however, GVHD rates in our patients (grade 3-4 acute GVHD, 14%; chronic GVHD, 44%) were similar to the rates reported in a recent Center for International Blood and Marrow Transplant Research study of younger patients undergoing high-dose conditioning before allogeneic HCT.[43] Infections in the absence of GVHD caused the deaths of 2% of our patients, suggesting a more rapid immune reconstitution in this cohort when compared with reduced-intensity conditioning regimens incorporating in vivo T-cell depletion, with reported infection-related mortality rates of 6% to 12%.[10,14]

The leading cause of treatment failure in previous studies of reduced-intensity conditioning regimens in patients with AML was relapse/progression, with 2- to 4-year relapse rates of 32% to 61%,[11,13,15,17] although a single-institution report by Mohty et al[12] described a 12% relapse rate at 4 years in 25 patients in CR1 undergoing reduced-intensity conditioning. Similarly, the leading cause of mortality in our study was relapse, with a 5-year estimated overall relapse/progression rate of 42%.

The current study showed higher relapse rates in patients with advanced disease, patients with unfavorable cytogenetics, and patients who underwent HCT within 6 months of diagnosis of AML. Furthermore, there was a suggestion of higher relapse/progression rates in patients with poor blood cell count recovery before HCT, which either represented impaired marrow function as a result of leukemia not detected by other methods, underlying myelodysplastic syndrome, or decreased hematopoietic reserve as a result of chemotherapy damage. Overall, our findings suggested that larger leukemia burden and perhaps faster proliferation rates associated with unfavorable cytogenetics enabled leukemic cells to outgrow GVL effects, a suggestion that was supported by the observation that more than half of the relapses occurred within 100 days of HCT. A previous report from our institution, investigating various hematologic malignancies at different disease stages, showed that graft-versus-tumor effects were most powerful in patients with relatively low tumor burden and more indolent tumors like chronic lymphocytic leukemia.[44]

Given the above observations regarding leukemia burden, it was surprising that MRD, while associated with higher risk of relapse in a univariate analysis, was no longer an independent risk factor when the multivariate analysis was adjusted to include cytogenetic risk. Most likely this was a result of the fact that a majority of patients (62%) with MRD had unfavorable cytogenetics, suggesting a codependency of these two variables. Furthermore, our observations are limited by relatively small patient numbers and variations in the techniques of disease assessment over time and among participating sites. Refinements in flow cytometry and molecular methods to assess leukemia burden and prognosis of AML (eg, *NPM1* mutation analysis reported by Schnittger et al[45]) will be important in the design of future studies.

In conclusion, allogeneic HCT from related or unrelated donors after nonmyeloablative conditioning resulted in long-term disease-free survival in patients with AML who were not considered candidates for myeloablative conditioning because of age or comorbid conditions. Best outcomes were observed in patients in CR1 or CR2 who had favorable/intermediate cytogenetic risks. New strategies will be required in patients with advanced AML and in patients with unfavorable cytogenetics with the aim of increasing GVL effects and thereby reducing relapse, which clearly has been the major cause of treatment failure.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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