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ORIGINAL REPORT

Reducing the Risk for Transplantation-Related Mortality After Allogeneic Hematopoietic Cell Transplantation: How Much Progress Has Been Made?

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ABSTRACT

Purpose
Transplantation-related mortality (TRM) is a major barrier to the success of allogeneic hematopoietic cell transplantation (HCT).

Patients and Methods
We assessed changes in the incidence of TRM and overall survival from 1985 through 2004 in 5,972 patients younger than age 50 years who received myeloablative conditioning and HCT for acute myeloid leukemia (AML) in first complete remission (CR1) or second complete remission (CR2).

Results
Among HLA-matched sibling donor transplantation recipients, the relative risks (RRs) for TRM were 0.5 and 0.3 for 2000 to 2004 compared with those for 1985 to 1989 in patients in CR1 and CR2, respectively ($P < .001$). The RRs for all causes of mortality in the latter period were 0.73 ($P = .001$) and 0.60 ($P = .005$) for the CR1 and CR2 groups, respectively. Among unrelated donor transplantation recipients, the RRs for TRM were 0.73 ($P = .095$) and 0.58 ($P < .001$) for 2000 to 2004 compared with those in 1990 to 1994 in the CR1 and CR2 groups, respectively. Reductions in mortality were observed in the CR2 group (RR, 0.74; $P = .03$) but not in the CR1 group.

Conclusion
Our results suggest that innovations in transplantation care since the 1980s and 1990s have reduced the risk of TRM in patients undergoing allogeneic HCT for AML and that this reduction has been accompanied by improvements in overall survival.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is an effective therapy for a variety of malignant and nonmalignant diseases. However, it carries a significant risk for treatment-related mortality, stemming primarily from infection,[1-3] conditioning regimen–related toxicities,[4-6] and graft-versus-host disease (GVHD).[7-9] The risk for transplantation-related mortality (TRM) is influenced by several factors, including patient age, donor type, and conditioning regimen intensity.[10-14] The risk of TRM varies from < 10% in children younger than age 10 years receiving HLA-matched related donor (MRD) transplantations to 30% or higher in adolescents and adults receiving unrelated donor (URD) transplantations.[10,11,13,14]

Since the 1980s, several innovations have been implemented to reduce TRM. More effective approaches for prevention of GVHD,[15] fungal infection, and cytomegalovirus (CMV) disease[16] have been introduced. Pharmacokinetic-based targeting of busulfan dosing has been adopted.[17] For patients receiving URD transplantations, enhancements have been made in HLA typing and matching.[18] At the same time, relevant advances have occurred in related fields, including critical care medicine, nephrology, and transfusion medicine.[19-21]

The collective impact of these advances on patient outcome is unknown. To address this matter, we assessed the change in TRM after transplantations for acute myeloid leukemia (AML), the most common indication for allogeneic HCT,[22] from 1985 to 2004.

Table 1. Characteristics of Patients With AML in CR1 or CR2 Who Received HLA-MRD or Matched URD Allogeneic HCT From 1985 to 2004

Characteristic	1985-1989		1990-1994		1995-1999		2000-2004		*P*
	No.	%	No.	%	No.	%	No.	%	
MRD/CR1 HCT									
No. of patients	1,124		1,283		901		460		—
Age, years									< .01
Median	27		30		31		31		
Range	1-50		1-50		1-50		1-50		
KPS ≥ 90	984	87	1,081	84	739	81	376	81	< .01
No comorbid conditions*	962	86	1,020	80	664	73	350	76	< .01
Cytogenetics†									< .01
Favorable	115	10	192	15	94	10	41	9	
Intermediate	326	39	506	39	508	56	304	66	
Poor	47	4	76	6	76	8	59	13	
Unknown	636	56	509	40	224	250	56	12	
Time from diagnosis to transplantation < 6 months	634	57	669	52	561	62	344	75	< .01
Bone marrow	1,124	100	1,279	99	662	73	199	43	< .01
Negative donor-recipient CMV match	319	28	371	29	287	32	97	21	< .01
BuCy	278	26	679	53	553	61	327	71	
GVHD prophylaxis									< .01
T-cell depletion	257	23	182	14	44	5	6	1	
CSA + MTX ± other	460	41	829	64	665	74	325	71	
CSA ± other (not MTX)	302	27	232	18	125	14	61	13	
Tacrolimus ± other	—		6	< 1	25	3	49	12	
Other	105	9	57	4	42	5	19	4	
Follow-up, months									
Median	148		112		83		35		
Range	3-257		3-207		2-141		3-85		
MRD/CR2 HCT									
No. of patients	202		232		202		124		
Age, years									< .01
Median	28		30		34		29		
Range	1-49		1-50		1-9		2-50		
KPS ≥ 90	166	82	174	75	147	73	98	79	.26
No comorbid conditions*	160	79	182	78	138	68	89	72	.03
Time from diagnosis to transplantation < 12 months	81	40	72	31	44	22	32	26	< .01
Cytogenetics†									< .01
Good	12	6	37	16	61	30	46	37	
Intermediate	43	21	69	30	80	40	52	42	
Poor	7	3	8	3	16	8	9	7	
Unknown	140	69	118	51	45	22	17	14	
Bone marrow	202		230	99	132	65	36	29	< .01
BuCy	70	35	127	55	131	65	92	74	< .01
Donor-recipient CMV match negative/negative	46	23	48	21	51	25	29	23	< .01
GVHD prophylaxis									< .01
T-cell depletion	47	23	22	9	13	6	2	2	
CSA + MTX	84	42	143	62	148	74	90	73	
CSA ± other (not MTX)	53	26	57	25	30	15	13	10	
Tacrolimus ± other	—		1	< 1	8	4	14	12	
Other	18	9	9	4	2	1	5	4	
Follow-up, months									
Median	146		115		93		48		
Range	3-251		5-200		3-151		3-86		
Matched URD/CR1 HCT									
No. of patients	—		82		230		440		—
Age, years	—								< .01
Median			26		29		30		
Range			1-50		1-50		1-50		
KPS ≥ 90	—		67	82	184	80	330	75	.20
No comorbid conditions*	—		69	84	181	79	268	61	< .01

(continued on following page)

Table 1. Characteristics of Patients With AML in CR1 or CR2 Who Received HLA-MRD or Matched URD Allogeneic HCT From 1985 to 2004 (continued)

Characteristic	1985-1989		1990-1994		1995-1999		2000-2004		*P*
	No.	%	No.	%	No.	%	No.	%	
Cytogenetics†									.08
Good	—		6	7	12	5	29	7	
Intermediate	—		43	52	140	61	232	53	
Poor	—		15	18	47	20	122	28	
Unknown	—		18	22	31	14	57	13	
Bone marrow	—		82	100	223	97	259	59	< .01
Negative donor-recipient CMV	—		33	40	65	28	127	29	< .01
BuCy	—		41	50	96	42	216	49	.19
HLA match status‡									< .01
Well matched	—		4	5	38	17	189	43	
Partially matched	—		30	37	140	61	215	49	
Mismatched	—		48	59	52	23	36	8	
GVHD prophylaxis									< .01
T-cell depletion	—		29	35	56	24	45	10	
CSA + MTX	—		46	56	151	66	239	54	
CSA ± other (not MTX)	—		5	6	4	2	25	5	
Tacrolimus ± other	—		1	1	17	8	123	28	
Other	—		1	1	2	< 1	7	3	
FU, months	—								
Median			139		98		44		
Range			51-207		8-144		3-97		
Matched URD/CR2 HCT									
No. of patients	—		107		300		380		—
Age, years	—								.02
Median			27		23		28		
Range			2-49		1-49		1-50		
KPS ≥ 90	—		85	79	230	77	278	73	.33
No comorbid condition	—		93	87	238	79	251	66	< .01
Time from diagnosis to transplantation < 12 months*	—		20	19	47	16	70	18	.70
Cytogenetics†									< .01
Good	—		12	11	88	29	92	24	
Intermediate	—		38	36	128	43	193	51	
Poor	—		9	8	16	5	30	8	
Unknown	—		48	45	68	23	65	17	
Bone marrow	—		106	99	294	98	249	66	< .01
BuCy	—		47	44	133	44	170	45	.96
HLA match status‡									< .01
Well matched	—		20	19	64	21	147	39	
Partially matched	—		27	25	174	58	184	48	
Mismatched	—		60	56	62	21	49	13	
Negative donor-recipient CMV	—		32	30	103	34	114	30	.50
GVHD prophylaxis									< .01
T-cell depletion	—		40	37	76	25	48	13	
CSA + MTX	—		49	46	184	61	194	51	
CSA ± other (not MTX)	—		14	13	5	2	24	6	
Tacrolimus ± other	—		2	2	33	11	109	29	
Other	—		2	2	2	1	5	1	
Follow-up, months	—								
Median			149		97		48		
Range			23-204		12-151		3-89		

Abbreviations: AML, acute myeloid leukemia; CR1, first complete response; CR2, second complete response; MRD, matched related donor; URD, unrelated donor; HCT, hematopoietic cell transplantation; KPS, Karnofsky performance score; CMV, cytomegalovirus; BuCy, busulfan/cyclophosphamide; GVHD, graft-versus-host disease; CSA, cyclosporine; MTX, methotrexate; FU, fluorouracil.

*Comorbid conditions are reported by the transplantation centers as any pre-existing medical condition present at time of transplantation.

†Cytogenetics are classified according to Slovak et al.[26a] Patients with normal cytogenetics are classified as having intermediate-risk disease.

‡Classification of HLA matching is based on Weisdorf et al[26] on assessment of HLA matching for retrospective studies.

PATIENTS AND METHODS

Patient-, Disease-, and Transplantation-Related Characteristics

Data on patients with AML who received mobilized peripheral blood or marrow HCT were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR). CIBMTR is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive HCTs to a statistical center located at the Medical College of Wisconsin (MCW) in Milwaukee, WI, and at the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis, MN. Participating centers are required to report all transplantations consecutively. Patients are followed longitudinally, with yearly follow-up. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensured data quality. Observational studies conducted by the CIBMTR were performed in compliance with the Privacy Rule (Health Insurance Portability and Accountability Act [HIPAA]) as a public health authority and in compliance with all applicable federal regulations pertaining to the protection of human research participants, as determined by continual review of the NMDP and MCW institutional review boards since 1985.

Patients age 50 years or younger with AML in first complete remission (CR1) or second complete remission (CR2) who received an HCT from an MRD from 1985 to 2004 or from a URD from 1990 to 2004 were eligible. All received bone marrow (BM) or peripheral blood progenitor cell (PBPC) grafts and myeloablative conditioning regimens based on busulfan/cyclophosphamide (BuCy) or cyclophosphamide/total-body irradiation (CyTBI).

End Points

The primary end point was TRM, defined as death during continuous complete remission. Overall survival (OS), leukemia-free survival (LFS), and leukemia relapse were also assessed.

Statistical Methods

Four groups defined by disease status at transplantation (CR1 and CR2) and donor type (MRD and URD) were formed. These groups, in turn, were separated into 5-year cohorts. Within each of the groups, patient-, disease-, and transplantation-related characteristics were compared by using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Probabilities of OS and LFS were calculated by using the Kaplan-Meier estimator.[23] For survival analyses, death from any cause was considered an event, and data on surviving patients were censored at last follow-up. For LFS analyses, relapse or death were considered an event, and data for patients alive in CR were censored at last follow-up. Probabilities of TRM and leukemia relapse were calculated by using the cumulative incidence function.[24] For TRM, relapse was the competing event and for relapse, TRM was the competing event. Data on patients without competing events were censored at last follow-up and CIs were calculated with a log transformation.[24]

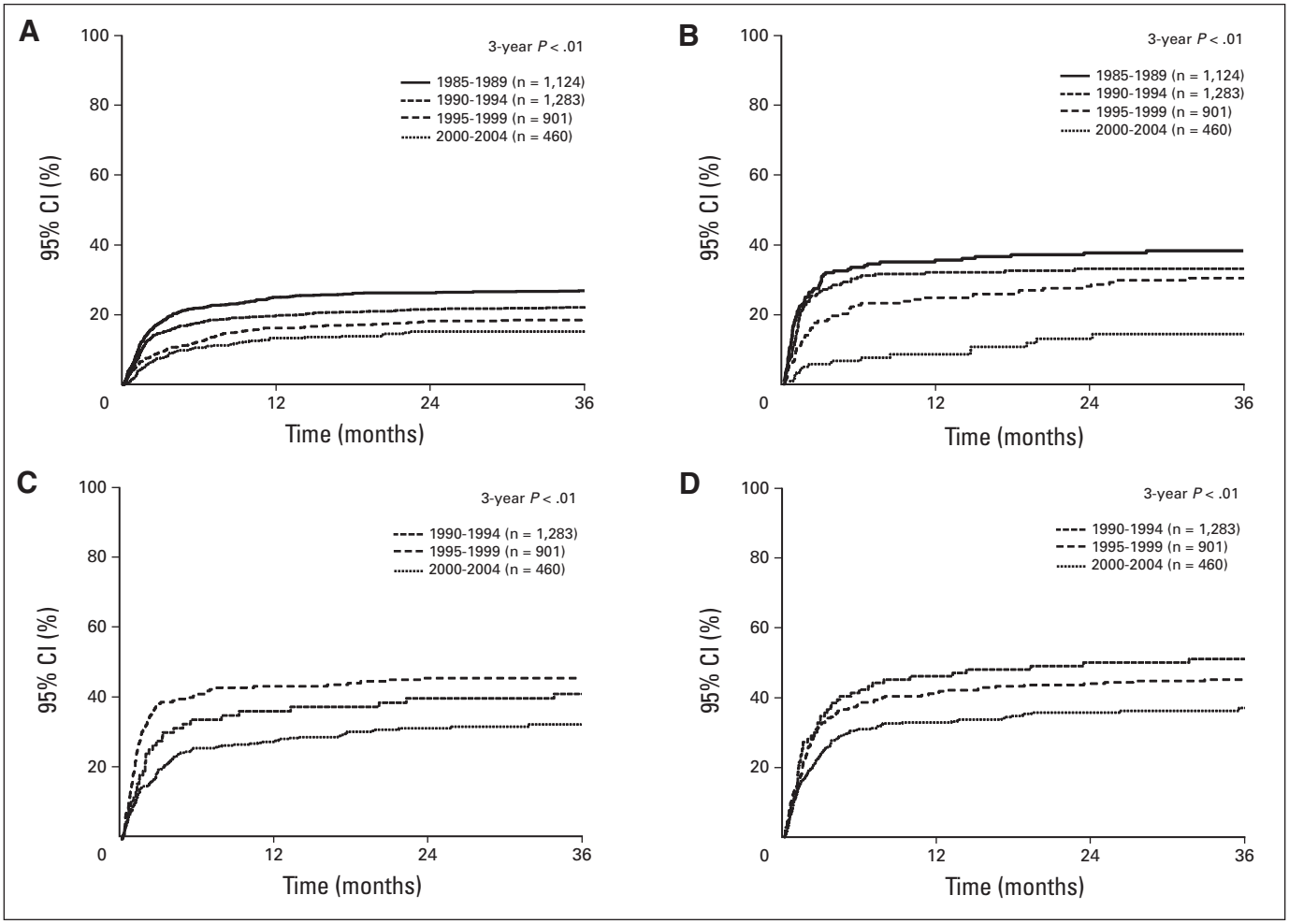

Fig 1. Transplantation-related mortality by 5-year periods. (A) Recipients of HLA-matched related donors in first complete remission, (B) recipients of matched related donors in second complete remission, (C) recipients of unrelated donors in first complete remission, and (D) recipients of unrelated donors in second complete remission.

The initial multivariate models were adjusted for patient characteristics only to avoid removing the effect of changes in practice. Cox proportional hazards regression[25] was used with a stepwise forward selection technique, in which year of transplantation was forced into the model and a P value $\leq .05$ was the criterion for other covariates to be included in the final model. Other patient characteristics considered in the analyses were comorbidities (the presence or absence of any comorbidity), recipient age, performance score at time of HCT, time from diagnosis to transplantation, sex, WBC count at diagnosis, and cytogenetics at diagnosis. Because of the possible confounding between unknown cytogenetics and year of transplantation, we fit models both with and without adjustment for cytogenetics; the results were similar in all cases. All possible risk factors were checked for proportional hazards by using a time-dependent covariate approach, and a stratified model was used when there were nonproportional hazards. First-order interactions between year of transplantation and other variables were assessed. Trend tests were used in the Cox model to test for the overall effect of year of transplantation. Adjusted probabilities of OS and LFS by year of transplantation were estimated by stratified Cox model. P values are two-sided. Analyses were done by using SAS software (SAS Institute, Cary, NC).

Additional exploratory multivariate analyses were done to investigate the impact of changes in select transplantation characteristics on changes in outcomes by year of transplantation, including donor-recipient sex and CMV serologic status, graft type (BM *v* PBPC), conditioning regimen (BuCy *v* CyTBI), GVHD prophylaxis (cyclosporine *v* tacrolimus-based), and HLA matching in the URD group.

URD-recipient pairs were classified according to the Weisdorf Criteria,[26] designed for use in retrospective studies that analyze HLA-matching data spanning many years. Weisdorf et al analyzed 21 subgroups of URD-recipient pairs whose matching varied from the three-loci low-resolution typing (A, B, DRB1) approach, common in the 1980s and early 1990s, to the four-loci high-resolution typing (A, B, C, DRB1) that is now standard. These subgroups clustered in three major groups according to survival analyses: well matched, partially matched, or mismatched.

Factors with sufficient overlap over time were included in the multivariate model in a stepwise fashion. Some factors (graft type, GVHD prophylaxis, HLA matching) changed dramatically over the study period. To avoid confounding, we conducted subgroup analyses examining the effect of year of transplantation in the largest groups of consistently treated patients over the years on the basis of those receiving BM, those receiving cyclosporine and methotrexate (CSA/MTX) for GVHD prophylaxis, and those receiving partially matched URD grafts.[26]

RESULTS

Patient-, Disease-, and Transplantation-Related Characteristics

Data were analyzed on 5,972 transplantations (3,704 MRD CR1, 750 MRD CR2, 738 URD CR1, 780 URD CR2; Table 1). Over time, changes in several patient, disease, and transplantation-related characteristics occurred. In the MRD CR1 group, patients were less likely to have a Karnofsky performance score (KPS) of at least 90 but were more likely to be $>$ 6 months from diagnosis. There was a decrease over time in the proportion of transplantations in which both the

Table 2. Univariate Probabilities of TRM by Age Among Patients With AML in CR1 Who Received HCT From an HLA-MRD and Overall TRM in Patients With AML in CR1 and CR2 Who Received MRD and URD HCT, Reported to the CIBMTR Between 1985 and 2004

	1985-1989			1990-1994			2000-2004			
Univariate Outcome	No. Evaluated	Probability	95% CI	No. Evaluated	Probability	95% CI	No. Evaluated	Probability	95% CI	*P*
TRM MRD/CR1 at 3 years by age group										
0-10	122	13	7 to 19	—	—	—	58	9	2 to 19	.229
11-20	218	22	17 to 28	—	—	—	83	7	2 to 13	< .001
21-30	339	27	22 to 31	—	—	—	86	10	4 to 18	< .001
31-40	316	32	27 to 37	—	—	—	101	16	10 to 24	.001
41-50	119	34	26 to 42	—	—	—	130	24	16 to 32	.199
TRM MRD/CR1 at:	1,114						458			
30 days		4	3 to 5	—	—	—		1	0 to 2	< .001
100 days		15	13 to 17	—	—	—		6	4 to 8	< .001
1 year		23	20 to 25	—	—	—		11	9 to 14	< .001
3 years		26	24 to 29	—	—	—		15	11 to 18	< .001
TRM MRD/CR2 at:	202						121			
30 days		10	7 to 15	—	—	—		1	0 to 3	< .001
100 days		25	19 to 31	—	—	—		5	2 to 10	< .001
1 year		35	28 to 41	—	—	—		8	4 to 13	< .001
3 years		37	31 to 44	—	—	—		13	7 to 20	< .001
TRM URD/CR1 at:	—			82			438			
30 days		—	—		7	3 to 14		5	3 to 8	.248
100 days		—	—		22	14 to 31		15	12 to 19	< .001
1 year		—	—		34	24 to 45		26	22 to 30	< .001
3 years		—	—		39	29 to 50		31	27 to 36	.002
TRM URD/CR2 at:	—			106			377			
30 days		—	—		8	3 to 13		7	4 to 9	.504
100 days		—	—		28	20 to 37		19	15 to 23	.028
1 year		—	—		44	35 to 54		31	27 to 36	.016
3 years		—	—		49	40 to 59		36	31 to 41	.019

Abbreviations: TRM, transplantation-related mortality; AML, acute myeloid leukemia; CR1, first complete remission; HCT, hematopoietic cell transplantation; MRD, matched related donor; CR2, second complete remission; URD, unrelated donor; CIBMTR, Center for International Blood and Marrow Transplant Research.

recipient and donor were serologically negative for CMV. In the MRD CR2 group, patients were less likely to have a transplantation within 12 months of diagnosis but were more likely to not have a comorbid condition at time of HCT. In both the MRD CR1 and MRD CR2 groups, BuCy was used more frequently for conditioning, and CSA/MTX was used more frequently for GVHD prophylaxis regimens in later periods. In the URD CR1 group, patients were less likely to be > 6 months from diagnosis over time. In both the URD CR1 and URD CR2 groups, patients were less likely to have a KPS of at least 90 and to receive T-cell depleted grafts in later time periods; they were more likely have a comorbid condition, to receive TBI-based conditioning and to have a well-matched donor. In all four groups, patients were more likely to have received a PBPC graft but were less likely to have unknown cytogenetic testing results in later periods.

TRM

Univariate analysis demonstrated a steady drop in 3-year incidence of TRM over time in both MRD groups. For patients in CR1, it dropped from 29% (95% CI, 24% to 29%) in the 1985 to 1989 period to 15% (95% CI, 11% to 18%) in the 2000 to 2004 period ($P < .001$). For patients in CR2, the TRM rate fell from 37% (95% CI, 31% to 44%) to 13% (95% CI, 7% to 20%) over the same time period ($P < .001$). In the URD CR1 group, the incidences of TRM were 39% (95% CI, 33% to 54%), 46% (95% CI, 39% to 52%), and 31% (95% CI, 27% to 36%; $P = .001$) for the periods 1990 to 1994, 1995 to 1999, and 2000 to 2004, respectively. In the URD CR2 group, the incidences of TRM during the same period were 49% (95% CI, 40% to 59%), 44% (95% CI, 38% to 50%), and 36% (95% CI, 31% to 41%), respectively ($P = .018$; Fig 1). Older age was associated with higher TRM in all four groups across all four time periods. The probability of TRM according to age and at different time points is shown in Table 2.

Adjusting for changes in patient and disease characteristics over time, the multivariate analyses demonstrated significant reductions in TRM over time in three of the four groups (Fig 2). In MRD HCT recipients, the relative risks (RRs) for TRM in 2000 to 2004 (compared with those in 1985 to 1989) were 0.5 (95% CI, 0.37 to 0.66; $P < .001$) and 0.25 (95% CI, 0.15 to 0.44; $P < .001$) for the CR1 group (adjusted for age, KPS, comorbid conditions, and cytogenetics) and CR2 group (adjusted for age), respectively. For URD HCT recipients, the RRs for TRM in 2000 to 2004 (compared with those in 1990 to 1994) were 0.73 (95% CI, 0.5 to 1.06; $P = .095$) and 0.58 (95% CI, 0.42 to 0.79; $P < .001$) for the CR1 group (adjusted for age) and CR2 group (adjusted for age and comorbid conditions), respectively. In the latter group, an interaction was observed between recipient age and year of transplantation; significant reductions in TRM occurred only in patients who were older than age 30 years.

When we examined the potential influences of specific changes in practice on the decrease in RR for TRM over time in the MRD/CR1, MRD/CR2, and URD/CR1 groups, adjustment for the effects of conditioning regimen and CMV serologic status had no significant impact (data not shown). In multivariate analyses restricted to BM recipients, the RRs for TRM were 0.6 (95% CI, 0.48 to 0.75; $P < .001$) and 0.43 (95% CI, 0.17 to 1.07; $P = .069$) in the 2000 to 2004 period compared with those in 1985 to 1990 in patients in the MRD/CR1 and MRD/CR2 groups, respectively. In BM recipients in the URD/CR1 group, the RR of TRM in 2000 to 2004 was 0.66 (95% CI, 0.47 to 0.92; $P = .016$) compared with 0.35 (95% CI, 0.22 to 0.55; $P < .001$) in 1990 to 1994. The RRs of TRM for patients who received CSA/MTX were 0.56 (95% CI, 0.38 to 0.81; $P = .002$), 0.35 (95% CI, 0.17 to 0.71; $P = .003$), and 0.35 (95% CI, 0.22 to 0.55; $P < .001$) in the MRD/CR1, MRD/CR2, and URD/CR1 groups in 2000 to 2004. For the URD/CR1 patients who received partially matched grafts, the RR of TRM in 2000 to 2004 was 0.64 (95% CI, 0.36 to 1.12; $P = .118$). The adjusted RR of TRM after MRD transplantation for selected subgroups is shown in Figure 3.

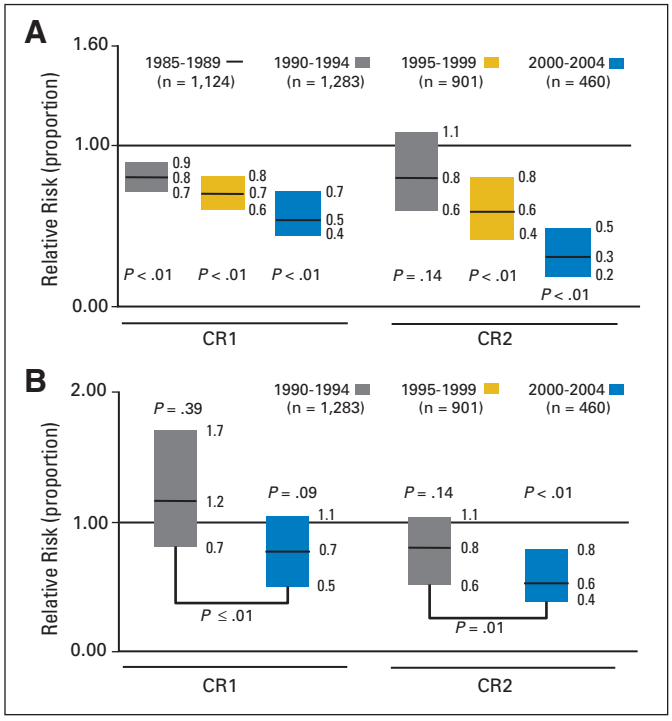

Fig 2. Transplantation-related mortality adjusted for patient and disease characteristics. (A) Recipients of HLA-matched related donor grafts and (B) recipients of unrelated donor grafts.

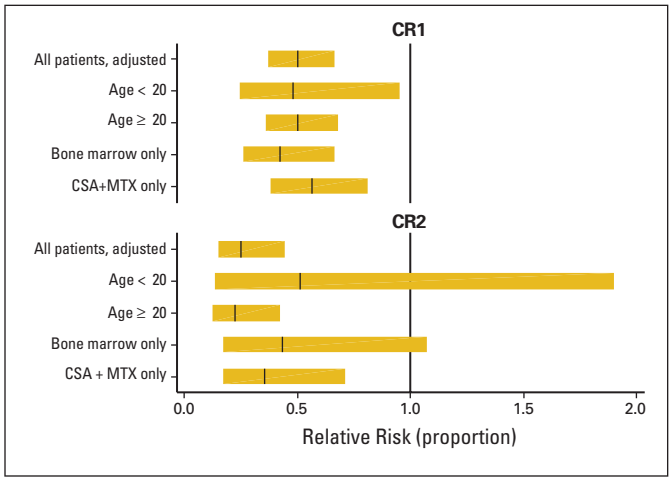

Fig 3. Transplantation-related mortality adjusted for patient and disease characteristics from 2000 to 2004 compared with that for 1985 to 1989 (baseline), among selected subgroups of HLA-identical sibling transplantation recipients with acute myeloid leukemia in first complete remission (CR1) and second complete remission (CR2). CSA, cyclosporine; MTX, methotrexate.

Leukemia Relapse, LFS, and OS

In the multivariate analysis, there were no significant differences in RR for relapse over time. Compared with the 1985 to 1989 baseline, the RRs of relapse in 2000 to 2004 were 1.09 (95% CI, 0.85 to 1.4; $P = .509$) for the MRD/CR1 patients, 1.25 (95% CI, 0.79 to 1.98; $P = .0.34$) for the MRD/CR2 patients, 1.3 (95% CI, 0.73 to 2.3; $P = .38$) for the URD/CR1 patients, and 1.21 (95% CI, 0.71 to 2.06; $P = .492$) for the URD/CR2 patients.

In the multivariate analyses for LFS, after adjustment for changes in patient and disease characteristics over time, RRs of treatment failure in the 2000 to 2004 period (compared with those in 1985 to 1989) were 0.75 (95% CI, 0.63 to 0.91; $P < .01$) in the MRD/CR1 group and 0.64 (95% CI, 0.45 to 0.90; $P = .01$) in the MRD/CR2 group. In the URD/CR1 group, the hazards for treatment failure were nonproportional. Adjusted probabilities of LFS at 1 year were 53% (95% CI, 42% to 64%) for the 1990 to 1994 period and 57% (95% CI, 52% to 62%; $P < .01$) for the 1990 to 1994 and 2000 to 2004 periods. Three-year probabilities of LFS were 46% (95% CI, 35% to 57%) and 45% (95% CI, 40% to 49%; $P = .36$), respectively. In the URD/CR2 group, the RR for treatment failure in 2000 to 2004 was 0.78 (95% CI, 0.59 to 1.03; $P = .077$) compared with that for 1990 to 1994. An interaction between transplantation period and age was noted; the RR was significant for the 41 to 50 years age group (RR, 0.46; 95% CI, 0.26 to 0.82; $P < .01$) but not the other groups (data not shown).

In the multivariate analyses for OS, after adjusting for changes in patient and disease characteristics over time, the RRs for all mortality causes for MRD HCT recipients were 0.73 (95% CI, 0.61 to 0.89; $P = .001$) for the CR1 group and 0.60 (95% CI, 0.42 to 0.86; $P = .005$) for the CR2 group in 2000 to 2004 compared with those for 1985 to 1989. In the URD/CR1 group, the hazards for all mortality causes were nonproportional (Fig 4). Adjusted probabilities of OS at 1 year were 56% (95% CI, 45% to 66%) for the 1990 to 1994 period and 63% (95% CI, 58% to 67%; $P = .02$) for the 2000 to 2004 period. Three-year probabilities of OS were 48% (95% CI, 37% to 59%) and 46% (95% CI, 41% to 51%; $P = .47$), respectively. In the URD/CR2 group, the RR for all mortality causes was 0.74 (95% CI, 0.56 to 0.97; $P = .031$) in 2000 to 2004 compared with that for 1990 to 1994. An interaction between year of transplantation and age was detected in the model for this group. The drop in mortality was greatest in patients older than age 40 years (RR, 0.46; 95% CI, 0.26 to 0.82). The impact of center on outcome was assessed and did not significantly influence the results (data not shown).

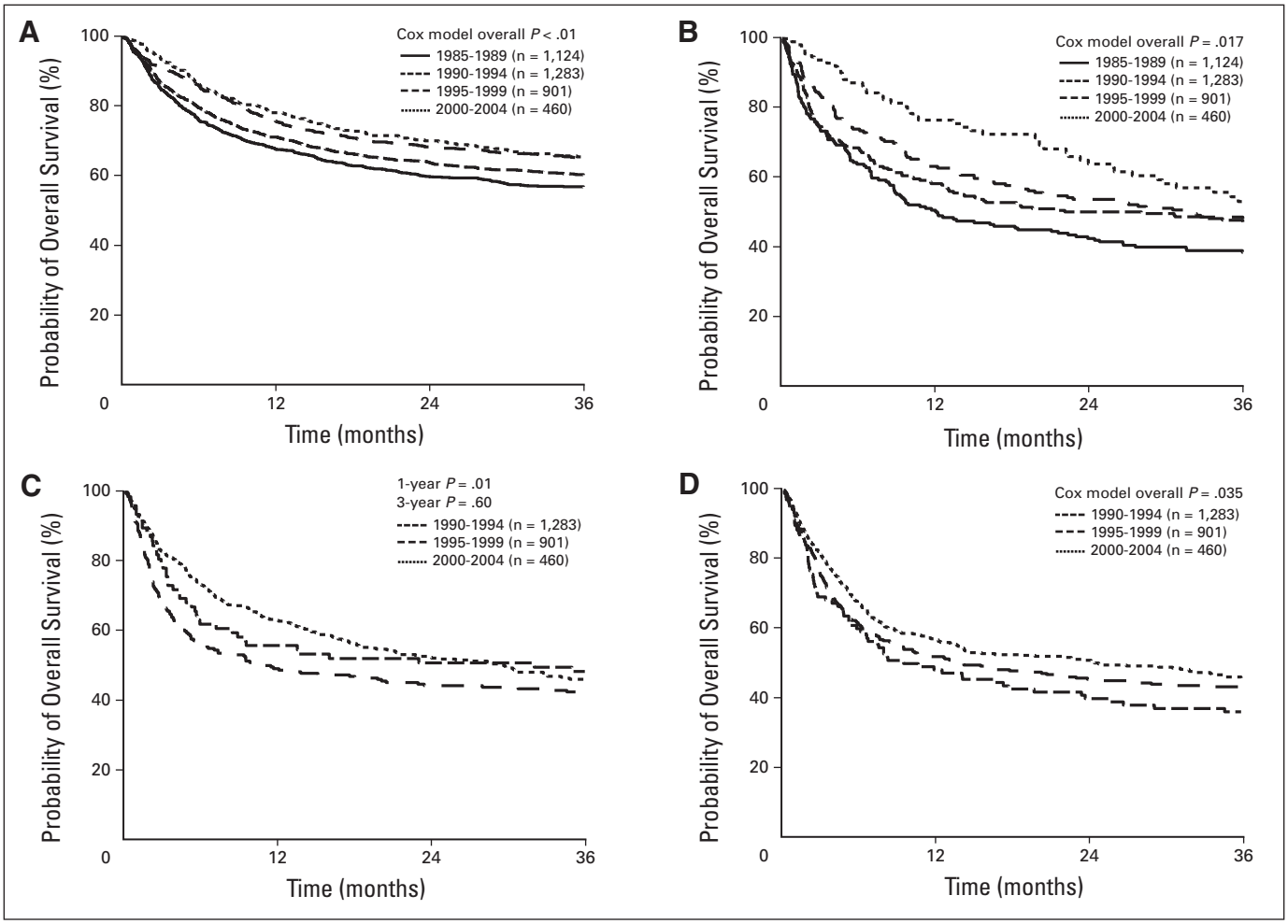

Fig 4. Adjusted overall survival by 5-year periods. (A) Recipients of HLA-matched related donors in first complete remission, (B) recipients of matched related donors in second complete remission, (C) recipients of unrelated donors in first complete remission, and (D) recipients of unrelated donors in second complete remission.

DISCUSSION

We observed a decline over time in the unadjusted probability of TRM after allogeneic transplantation using myeloablative conditioning for patients with AML who were younger than age 50 years. Since our primary objective was to estimate the collective impact of changes in transplantation practice on the risk for TRM, we calculated rates that were adjusted for changes in relevant patient and disease characteristics. Reductions in TRM remained significant in three of the four groups (MRD/CR1, MRD/CR2, URD/CR2), suggesting that changes in practice rather than patient characteristics were the primary factors driving the decrease in risk for TRM.

An alternative explanation for the decrease in the incidence of TRM is that improvements in the pretransplantation health of HCT recipients occurred over time, making them less susceptible to complications. Such an improvement could have arisen either through advances in supportive care during chemotherapy or perhaps through more discriminating selection of patients for transplantation. Although such an improvement could have contributed to the reduction in TRM, it is unlikely to be the sole cause. First, the proportions of patients with poor performance status or a comorbid condition in each group either increased over time or remained stable. Second, we adjusted for changes in patient and disease characteristics over time to isolate the effect of changes in practice. Finally, recognizing the potential selection bias that the increase in the use of reduced-intensity conditioning regimens for patients who are marginal candidates for myeloablative conditioning might engender, we chose to study younger patients for whom myeloablative conditioning remains the norm.

An important finding in our study is that for the three groups in which the adjusted risk for TRM decreased over time, there was an accompanying improvement in survival. Although the reduction in TRM and improvement in survival are encouraging, our results also draw attention to the fact that the risk for TRM after allogeneic HCT remains high, especially after URD transplantation.

Since the 1980s, there has been a steady succession of innovations designed to reduce the risk of TRM. More effective cyclosporine-based GVHD prophylaxis was adopted in the 1980s.[27] In the 1990s, another calcineurin inhibitor, tacrolimus, was introduced,[28] and other innovations occurred, including the introduction of fluconazole prophylaxis to prevent invasive fungal infections,[29,30] leukocyte reduction of blood products, new screening assays to prevent CMV disease,[16,19] and busulfan pharmacokinetic testing.[17] Since 2000 there have been other advances, including the adoption of broader, molecularly defined HLA matching for the selection of URDs.[18] In addition, in the last decade, PBPCs have largely supplanted BM for adults undergoing MRD HCT for hematologic malignancies, although its overall impact on TRM has been ambiguous.[31,32] A limitation of our study, which relied on data from the CIBMTR, was the inability to directly gauge the impact of these and other individual innovations. We were able to indirectly estimate the effect of a limited set of changes by subgroup analysis and other means and did not identify any specific advance or advances that were primarily responsible for the reduction in TRM.

We believe that our results in AML can be generalized to other diseases in which HCT with myeloablative conditioning is performed since the causes of TRM are largely the same regardless of indication for transplantation. This is substantiated by the results of a large Italian single-center trial that demonstrated reductions in TRM over time in patients with a variety of hematologic malignancies.

Advances that hold the potential to further reduce the risk of TRM in patients undergoing HCT continue to be made. The recent identification of risk factors based on comorbidity and serum levels of biomarkers of inflammation, for example, now permits more careful patient selection.[33,34] Ongoing studies may yield further gains. For example, genome-wide testing for genetic susceptibilities to the various causes of TRM is being performed using URD-recipient pair samples and data from the CIBMTR (personal communication, Theresa Hahn, August 2010). Such research may make it possible to minimize TRM by tailoring the transplantation approach to individual patients.

Our results indicate that the risk of leukemic relapse, unlike TRM, has not improved over time. Therefore, continued research toward enhancing the antileukemic effect of HCT is needed.

In conclusion, the risk for TRM in patients receiving myeloablative conditioning and allogeneic transplantation for AML has decreased since the 1980s, and this reduction appears to be primarily attributable to changes in practice.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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