Comparable survival after HLA-well-matched unrelated or matched sibling donor transplantation for acute myeloid leukemia in first remission with unfavorable cytogenetics at diagnosis

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We compared the outcomes of unrelated donor (URD, n = 358) with human leukocyte antigen (HLA)–matched sibling donor (MSD, n = 226) transplantations in patients with acute myeloid leukemia (AML) in first complete remission (CR1) having unfavorable cytogenetics at diagnosis. Unfavorable cytogenetic abnormalities were: complex (≥ 3 abnormalities), 32%; and noncomplex involving chromosome 7, 25%; chromosome 5, 9%; 11q or MLL rearrangements, 18%; t(6;9), 5%; and other noncomplex, 10%. URDs were HLA-well-matched (n = 254; 71%) or partially-matched (n = 104; 29%). Three-year leukemia-free survival (LFS) for MSD was 42% (95% confidence interval [CI], 35%-48%) compared with 34% (95% CI, 28%-41%) for HLA-well-matched URD and 29% (95% CI, 20%-39%) for partially-matched URD (*P* = .08). In multivariate analysis, HLA-well-matched URD and MSD yielded similar LFS (relative risk [RR] = 1.1, 95% CI, 0.86-1.40, *P* = .44) and overall survival (OS; RR = 1.06, 95% CI, 0.83-1.37, *P* = .63). LFS and OS were significantly inferior for HLA-partially-matched URD recipients, those with prior myelodysplastic syndrome, and those older than 50 years. All cytogenetic cohorts had similar outcomes. Patients with chronic graft-versus-host disease had a significantly lower risk of relapse (RR = 0.68, 95% CI, 0.47-0.99, *P* = .05). Hematopoietic cell transplantation (HCT) using HLA-well-matched URD and MSD resulted in similar LFS and OS in AML patients in CR1 with unfavorable cytogenetics. Outcomes of HCT from HLA-partially-matched URD were inferior. (*Blood*. 2010; 116(11):1839-1848)

Introduction

The role of allogeneic hematopoietic cell transplantation (HCT) using matched sibling donor (MSD) has been extensively investigated in patients with acute myeloid leukemia (AML) in first complete remission (CR1). However, if an MSD is not available, the role of unrelated donor (URD) HCT in AML CR1 is not well defined. A meta-analysis of 5 prospective biologic assignment studies comparing the role of HCT with non-HCT treatments in AML patients in CR1 demonstrated a beneficial effect of HCT for patients with unfavorable cytogenetics and recommended HCT for AML patients with unfavorable cytogenetics if an MSD is available.[1] A recent systematic review and meta-analysis of prospective biologic assignment studies analyzed 3638 patients with AML in CR1 by cytogenetic risk and showed significant survival benefit of HCT for those with intermediate and unfavorable cytogenetics.[2] Most patients in these studies underwent HCT using MSD and published comparisons of URD HCT to either nonallogeneic treatments or MSD transplantations, particularly for these higher risk subgroups, are limited.[3,4] Treatment-related complications and treatment-related mortality (TRM) were worse with URD HCT in the early studies for patients with leukemias.[5,6] Recent studies comparing MSD with URD in AML are limited by the small number of patients in CR1.[7-10] The guidelines of various major organizations in Europe and the United States on the use of alternative donors for AML patients in CR1 are not consistent: European Group for Blood and Marrow Transplantation, European Society for Medical Oncology, British Committee for Standards in Hematology, American Society of Blood and Marrow Transplantation, and National Comprehensive Cancer Network.[11-16] These assessments have led to different practices for use of URD HCT for AML patients in CR1.

High-resolution human leukocyte antigen (HLA) typing has improved donor selection and correspondingly the success of URD HCT.[17-19] We therefore sought to determine the impact of donor type on the outcomes of transplantation in patients with AML CR1 with unfavorable cytogenetics, a high-risk AML considered as a potential indication for either MSD or URD HCT.

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Methods

Data sources

Data were obtained from the statistical center of the Center for International Blood and Marrow Transplant Research (CIBMTR). More than 500 transplantation centers worldwide contribute detailed data on consecutive allogeneic and autologous HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis using established techniques for follow-up and data verification. Observational studies conducted by the CIBMTR are carried out with a waiver of informed consent in accordance with the Declaration of Helsinki and in compliance with Health Insurance Portability Accountability Act regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

Study population

The study population consisted of patients with AML in CR1 who had unfavorable cytogenetics and underwent first HCT using MSD or URD between 1995 and 2006. Patients with cord blood transplantations (n = 49), other related family donor (n = 40), and mismatched URD or unknown HLA matching (n = 59) were excluded. In addition, patients with acute promyelocytic leukemia (n = 3) and those who received HCT more than 12 months from CR1 (n = 35) were excluded.

URD transplant recipients were classified based on available HLA typing as previously described.[20] According to this classification, HLA-well-matched was defined as no known disparity at HLA-A, -B, -C, or -DRB1 and partially-matched as one locus known or probably disparate with the donors. Conditioning regimens were defined as myeloablative and reduced intensity using the criteria defined by the CIBMTR.[21]

Cytogenetics

Unfavorable cytogenetics were defined according to the Southwest Oncology Group/Eastern Cooperative Oncology Group (SWOG/ECOG) classification[22] and included: del(5q)/−5, −7/del(7q), abnormality 3q, 9q, 11q, 20q, 21q, 17p, t(6;9), t(9;22), and complex cytogenetics (≥ 3 unrelated abnormalities). Cytogenetics results were reviewed as provided by the transplantation center. Abnormalities were further classified as either complex cytogenetics (≥ 3 unrelated abnormalities) or noncomplex, further subcategorized as abnormalities of chromosome 7, chromosome 5, 11q or MLL gene rearrangements, t(6;9), and other noncomplex changes.

Endpoints

Primary endpoints were TRM, graft-versus-host disease (GVHD), relapse, leukemia-free survival (LFS), and overall survival (OS) calculated from the date of HCT. TRM was defined as death during continuous CR. Acute and chronic GVHD was diagnosed and graded by the transplantation center according to defined criteria.[23,24] Relapse was defined as hematologic leukemia recurrence. For analyses of LFS, treatment failure was leukemia relapse or death from any cause. For OS, failure was death from any cause. Surviving patients were censored at the last follow-up.

Statistical methods

Patient-, disease-, and transplantation-related variables for patients undergoing MSD and URD HCT were compared using the χ^2 statistic for categorical variables and the Kruskal-Wallis test for continuous variables. Probabilities of acute and chronic GVHD, TRM, and leukemia relapse were calculated using cumulative incidence curves to accommodate competing risks. Univariate probabilities of LFS and OS were calculated using the Kaplan-Meier estimator; the log-rank test was used for univariate comparisons between the groups.[25]

Assessments of potential risk factors for outcomes of interest were evaluated in multivariate analyses using Cox proportional hazards regression.[26] A stepwise model selection approach was used to identify all significant risk factors. Each step of model building contained the main effect of donor type. Factors that were significant at a 5% level were kept in the final model. Potential interactions between the main effect and all other significant risk factors were tested. A significant interaction was found between age and conditioning regimen, so that a combined age and conditioning intensity variable was considered: age less than 20 years, age 20 to 50 years myeloablative, age 20 to 50 years reduced-intensity conditioning (RIC), age more than 50 years myeloablative, and age more than 50 years RIC.

The proportionality assumption was tested by including a time-dependent covariate for each factor. When a test indicated differential effects over time (nonproportional hazards), models were constructed breaking the posttransplantation course into 2 time periods, using the maximized partial likelihood method to find the most appropriate breakpoint. Proportionality assumptions were then tested on each time period. After the aforementioned modeling of time-varying effects, the final multivariate model was built. The effects of acute or chronic GVHD on relapse, LFS, and OS were assessed using time-dependent covariates in the final Cox model.

Variables considered in the multivariate analysis

In addition to the donor type and degree of HLA match (MSD vs well-matched URD vs partially matched URD), which was included in all the models, the following variables were considered: patient age in years (< 20 vs 20-50 vs > 50), sex, performance scores (≥ 90% vs < 90% vs missing), white blood cell count at diagnosis ($\leq 50 \times 10^9$/L vs $> 50 \times 10^9$/L vs missing), interval from diagnosis to transplantation (< 3 months vs 3-6 months vs 6-9 months vs > 9 months), extramedullary leukemia, central nervous system disease before HCT, therapy-related AML, prior myelodysplastic syndrome (MDS), cytogenetic abnormalities (complex abnormalities vs chromosome 7 abnormalities vs chromosome 5 abnormalities vs 11q or MLL gene rearrangement vs t(6;9) vs other noncomplex), fungal infection before HCT, conditioning regimen (myeloablative vs RIC), combined age and conditioning intensity variables described in "Statistical methods," donor-recipient sex match (male-male vs male-female vs female-male vs female-female), donor-recipient cytomegalovirus status (−/− vs +/− vs −/+ vs +/+), graft type (bone marrow vs peripheral blood progenitor cells [PBPCs]), year of transplantation (by 2-year time periods), GVHD prophylaxis (cyclosporine A ± others vs tacrolimus ± other vs T-cell depletion vs others/none), antithymocyte globulin given as part of conditioning or GVHD prophylaxis, and the administration of myeloid growth factors to promote engraftment.

Results

Patient, disease, and transplantation characteristics

A total of 584 patients from 151 transplantation centers met the study eligibility criteria: 226 were MSD and 358 were URD HCT recipients. Among the URD transplantation recipients, 254 (71%) were HLA-well-matched with their donors and 104 (29%) were partially matched. Median follow-up of survivors was 44 months (range, 3-135 months).

Table 1 shows the patient, disease, and transplantation characteristics of the study patients. Cytogenetic abnormalities were: complex abnormalities (≥ 3 unrelated abnormalities), 32%; and noncomplex including abnormalities of chromosome 7, 25%; chromosome 5, 10%; 11q or MLL gene rearrangements, 18%;

t(6;9), 5%; and other noncomplex abnormalities, 10%. A higher proportion of patients undergoing URD HCT had complex cytogenetics (41% vs 18%, $P < .001$).

Transplantation outcomes

GVHD. The cumulative incidence of acute grade 2 to 4 GVHD at 100 days was 38% (95% confidence interval [CI], 31%-44%), 54% (95% CI, 48%-60%), and 52% (95% CI, 42%-61%) in patients undergoing MSD, HLA-well-matched URD, and partially-matched URD HCT, respectively (Table 2). Severe acute GVHD (grade 3 or 4) was significantly less frequent in patients undergoing MSD and HLA-well-matched URD HCT compared with partially-matched URD transplantation: 19% (95% CI, 13%-23%), 25% (95% CI, 19%-30%), versus 33% (95% CI, 23%-41%; $P = .02$). In patients alive at 100 days, the cumulative incidence of chronic GVHD at 3 years was 43% (95% CI, 36%-50%), 59% (95% CI, 52%-66%), and 54% (95% CI, 41%-66%) in patients undergoing MSD, HLA-well-matched URD, and partially-matched URD transplantation, respectively (Table 2). Chronic GVHD was significantly more frequent after well-matched URD versus MSD HCT ($P = .002$).

TRM. In univariate analysis, the cumulative incidence of TRM at 3 years was 21% (95% CI, 16%-27%), 26% (95% CI, 21%-32%), and 47% (95% CI, 37%-56%) in patients undergoing MSD, HLA-well-matched URD, and partially-matched URD transplantation, respectively (Table 2; Figure 1A). In multivariate analysis (Table 3), TRM was significantly higher in URD transplantations (HLA-well-matched or partially-matched) compared with MSD transplantations: HLA-well-matched URD, relative risk (RR) = 1.55 (95% CI, 1.02-2.37), $P = .04$; partially-matched URD, RR = 3.03 (95% CI, 1.94-4.75), $P < .001$. Independent of donor type, TRM was higher with a prior history of MDS, use of growth factor to promote engraftment, GVHD prophylaxis, graft type, age, and conditioning regimen (Table 3).

TRM was significantly lower in patients receiving tacrolimus-based GVHD prophylaxis compared with cyclosporine A–based prophylaxis (RR = 0.45, $P = .01$) but was similar with T-cell depletion (RR = 1.07). Patients undergoing PBPC transplantations had lower TRM in the first 3 months after transplantation (RR = 0.55, $P = .03$), but similar TRM beyond 3 months after transplantation (RR = 1.16, $P = .56$). TRM was significantly higher after 3 months after transplantation in patients older than 50 years undergoing either myeloablative conditioning (RR = 2.66, $P < .001$) or RIC (RR = 2.84, $P < .001$; Table 3). In patients older than 50 years, TRM was similar after either myeloablative or RIC ($P = .84$).

Relapse. In univariate analysis, the cumulative incidence of relapse at 3 years was 37% (95% CI, 31%-44%), 40% (95% CI, 33%-46%), and 24% (95% CI, 16%-33%) in patients undergoing MSD, HLA-well-matched URD, and partially-matched URD transplantation, respectively (Table 2; Figure 1B). In multivariate analysis (Table 3), no effect of donor type on relapse was observed. Donor-recipient sex matches and age/conditioning regimen were factors associated with relapse. Relapse was less frequent in male recipients of female donor grafts (RR = 0.48, $P < .001$) compared with male recipients of male donor grafts. Patients older than 50 years undergoing RIC had significantly more relapses compared with other groups (Table 3). In patients older than 50 years, the relapse rate after RIC was significantly higher than after myeloablative conditioning ($P < .001$). Chronic, but not acute, GVHD was associated with significantly lower risks of relapse: RR = 0.68 (95% CI, 0.47-0.99), $P = .046$.

LFS

In univariate analysis, LFS at 3 years was 42% (95% CI, 35%-48%), 34% (95% CI, 28%-41%), and 29% (95% CI, 20%-39%) in patients undergoing MSD, HLA-well-matched URD, and partially-matched URD transplantation, respectively (Table 2; Figure 1C). In multivariate analysis (Table 4), LFS was similar after MSD and HLA-well-matched URD transplantations (RR = 1.1, $P = .114$), whereas partially-matched URD transplantations had inferior LFS (RR = 1.38, $P = .038$). Other independent factors for LFS were prior history of MDS, graft type, and age/conditioning regimens. The beneficial effect of PBPC on LFS was only seen in the first 3 months after transplantation (first 3 months, RR = 0.6, $P = .016$; after 3 months, RR = 0.96, $P = .79$). Age/conditioning regimen had a significant impact on LFS beyond 3 months with inferior outcomes in patients older than 50 years undergoing either myeloablative (RR = 1.7, $P = .005$) or RIC (RR = 2.56, $P < .001$). Patients older than 50 years undergoing RIC had significantly inferior LFS compared with those receiving myeloablative conditioning ($P = .051$).

Survival

In univariate analysis, OS at 3 years was 45% (95% CI, 38%-52%), 37% (95% CI, 31%-44%), and 31% (95% CI, 22%-41%) in patients undergoing MSD, HLA-well-matched URD, and partially-matched URD transplantation, respectively (Table 2; Figure 1D). In multivariate analysis (Table 4), OS was similar in MSD and HLA-well-matched URD transplantations (RR = 1.06, $P = .62$), whereas partially matched URD transplantations had inferior outcomes (RR = 1.42, $P = .026$). Other factors associated with OS were therapy-related AML, donor/recipient sex match, graft type, and age/conditioning regimen. Patients with therapy-related AML and male-to-male donor/recipient combination had inferior OS. The beneficial effect of PBPC on OS was mainly seen in the first 3 months after transplantation. No impact of age and conditioning was seen on OS in the first 3 months after HCT, whereas survival was significantly inferior in patients older than 50 years undergoing either myeloablative (RR = 1.82, $P = .001$) or RIC (RR = 2.88, $P < .001$). In patients older than 50 years, OS of patients undergoing myeloablative conditioning was superior compared with those undergoing RIC ($P = .02$).

Acute GVHD had an adverse impact on both LFS (RR = 1.53, $P < .001$) and OS (RR = 1.78, $P < .001$), whereas chronic GVHD did not influence either LFS (RR = 1.11, $P = .48$) or OS (RR = 0.91, $P = .5$; Table 4).

Impact of cytogenetic abnormalities on outcomes

No significant differences in relapse were observed among the various cytogenetic subsets. The cumulative incidence of relapse at 3 years in patients with complex cytogenetics, abnormalities of chromosome 7, chromosome 5, 11q, or MLL gene rearrangement, t(6;9), and other noncomplex abnormalities were 40% (95% CI, 32%-47%), 30% (95% CI, 22%-38%), 42% (95% CI, 28%-54%), 39% (95% CI, 29%-49%), 30% (95% CI, 14%-48%), and 33% (95% CI, 21%-46%), respectively (Figure 2). There were no significant differences in TRM, LFS, and OS among cytogenetic subsets (data not shown).

Table 1. Patient-, disease-, and transplantation-related characteristics

Characteristic	All patients, n (%)	Matched sibling donor, n (%)	URD, n (%)	*P*
No. of patients	584	226	358	
No. of centers	151	94	102	
Median age (range), y	43 (< 1-74)	40 (1-74)	45 (< 1-73)	.01
Age at transplantation, y				.02
Younger than 20	88 (16)	45 (20)	43 (12)	
20-49	296 (50)	113 (50)	183 (51)	
50 or older	200 (34)	68 (30)	132 (37)	
Male sex	326 (56)	132 (59)	191 (53)	
Karnofsky score before HCT, < 90%	136 (25)	53 (23)	83 (23)	
Missing	38	4	34	
WBC at diagnosis, $\times 10^9$/L				
Median, range	5.4 (< 1-700)	6 (< 1-700)	4.4 (< 1-354)	.02
Less than 50	473 (86)	176 (82)	297 (88)	
50 or more	76 (14)	38 (18)	38 (12)	
Missing	35	12	23	
Extramedullary leukemia	35 (6)	18 (8)	17 (5)	
CNS disease before transplantation				.004
Yes	14 (2)	11 (5)	3 (1)	
No	570 (98)	215 (95)	355 (99)	
Therapy-related leukemia				
Yes	84 (14)	25 (11)	59 (16)	
Missing	5	4	1	
Prior myelodysplasia				
Yes	111 (19)	35 (15)	76 (21)	
Missing	4	3	1	
Time from diagnosis to transplantation, mo				
Median (range)	5 (1-40)	4 (1-40)	5 (1-14)	< .001
Less than 3	62 (11)	35 (15)	27 (8)	< .001
3-6	366 (63)	149 (66)	217 (61)	
6-9	115 (20)	30 (13)	85 (24)	
More than 9	41 (7)	12 (5)	29 (8)	
Cytogenetics abnormality				< .001
Complex (≥ 3 unrelated abnormalities)	187 (32)	41 (18)	146 (41)	
Chromosome 7 abnormalities	148 (25)	55 (23)	93 (26)	
Chromosome 5 abnormality	58 (10)	26 (12)	32 (9)	
MLL gene rearrangement	104 (18)	55 (25)	49 (13)	
t(6;9)	28 (5)	18 (8)	10 (3)	
Other noncomplex abnormalities	59 (10)	31 (14)	28 (8)	
Fungal infection anytime before HCT				
Yes	102 (17)	31 (14)	71 (20)	
Missing	8	6	3	
Conditioning regimen				.004
Myeloablative	435 (74)	183 (81)	252 (70)	
Reduced intensity	149 (26)	43 (19)	106 (30)	
Median donor age, y (range)	35 (1-74)	38 (1-74)	34 (19-60)	.02
Donor-recipient sex match				.03
Male-male	214 (37)	79 (35)	135 (38)	
Male-female	155 (27)	50 (22)	105 (30)	
Female-male	111 (19)	56 (25)	55 (15)	
Female-female	102 (17)	41 (18)	61 (17)	
Missing	2	0	2	
Donor-recipient CMV serostatus				< .001
+/+	153 (26)	80 (37)	73 (20)	
+/−	60 (10)	25 (12)	35 (10)	
−/+	198 (36)	54 (25)	144 (41)	
−/−	159 (28)	57 (26)	102 (29)	
Missing	14	10	4	
Type of donor				
HLA-identical sibling	226 (39)	226 (100)	0	
URD well-matched	254 (43)	0	254 (71)	
URD partially matched	104 (18)	0	104 (29)	

CNS indicates central nervous system; Tac, tacrolimus; CsA, cyclosporine A; and ATG, antithymocyte globulin.

Table 1. Patient-, disease-, and transplantation-related characteristics (continued)

Characteristic	All patients, n (%)	Matched sibling donor, n (%)	URD, n (%)	*P*
Graft type				
Bone marrow	239 (41)	89 (39)	184 (44)	
Peripheral blood progenitor cells	345 (59)	137 (61)	232 (56)	
Year of transplantation				< .001
1995-2000	160 (27)	106 (47)	54 (15)	
2001-2006	424 (73)	120 (53)	304 (85)	
Growth factor used to promote engraftment				< .001
Yes	190 (39)	73 (35)	117 (42)	
No	297 (61)	136 (65)	161 (58)	
Missing	97	17	80	
ATG given as conditioning or GVHD prophylaxis	114 (20)	18 (8)	96 (27)	< .001
GVHD prophylaxis				< .001
CsA ± others	292 (50)	155 (68)	137 (38)	
Tac ± others	231 (40)	40 (18)	191 (53)	
T-cell depletion	49 (8)	20 (9)	29 (8)	
Others/missing	12 (2)	11 (5)	1 (1)	
Median follow-up of survivors, mo (range)	44 (3-135)	61 (3-131)	35 (3-135)	

CNS indicates central nervous system; Tac, tacrolimus; CsA, cyclosporine A; and ATG, antithymocyte globulin.

Discussion

In this large analysis of HCT for CR1 AML with unfavorable cytogenetics, we demonstrate similar LFS and OS with MSD and HLA-well-matched URD. HCT during CR1 provides sustained remission and survival for approximately 34% to 42% of these high-risk patients. A majority of cytogenetically high-risk AML patients treated with consolidation therapy relapse within a year and 4-year LFS is reported as 17% to 18%.[27,28] Promising extended LFS with HCT and the observed beneficial effect of chronic GVHD on relapse suggest a potent graft-versus-leukemia effect, even in these high-risk leukemias.

Our findings have important implications for the management of high-risk patients with AML in CR1. As MSDs are identified only for a small proportion of patients, the pool of patients who may benefit from HCT may be considerably expanded using well-matched URD for HCT. Even for those lacking allele-matched URD, partially matched URD HCT yielded 29% 3-year LFS, which appears acceptable, given their worse prognosis with chemotherapy alone. There were no significant differences in relapse after MSD, well-matched URD, or partially-matched URD

Table 2. Post-HCT outcomes: univariate analysis

Outcome event	Matched sibling donor, incidence (95% CI)	Well-matched URD, incidence (95% CI)	Partially-matched URD, incidence (95% CI)	*P*, overall	*P*, MSD vs well-matched URD	*P*, well-matched URD vs partially-matched URD
Acute GVHD, grades 2-4, 100 d	38 (31-44)	54 (48-60)*	52 (42-61)	< .001	< .001	NS
Chronic GVHD†						
1 y	39 (32-46)	54 (47-61)*	50 (37-61)	.007	.002	.53
3 y	43 (36-50)	59 (52-66)*	54 (41-66)	.007	.002	.50
TRM						
100 d	8 (5-12)	11 (7-15)	26 (18-35)	< .001	NS	.001
3 y	21 (16-27)	26 (21-32)	47 (37-56)	< .001	NS	< .001
Relapse						
1 y	29 (23-35)	35 (29-41)	20 (13-29)	.015	NS	.004
3 y	37 (31-44)	40 (33-46)	24 (16-33)	.013	NS	.004
LFS						
1 y	54 (47-61)	46 (39-52)	37 (27-46)	.01	.06	.14
3 y	42 (35-48)	34 (28-41)	29 (20-39)	.08	.11	NS
OS						
1 y	63 (56-69)	54 (48-60)	42 (32-51)	.001	.06	.03
3 y	45 (38-52)	37 (31-44)	31 (22-41)	.07	.13	NS

Data are cumulative incidence (for GVHD, TRM, and relapse) or Kaplan-Meier estimates (LFS and OS; 95% confidence interval) for outcomes.
NS indicates pairwise comparisons that were not statistically significant ($P > .15$).
*Significantly different ($P < .05$) outcomes (acute and chronic GVHD) between MSD and well-matched URD. All other comparisons between these 2 subgroups were NS.
†Calculated for patients surviving 100 days after transplantation.

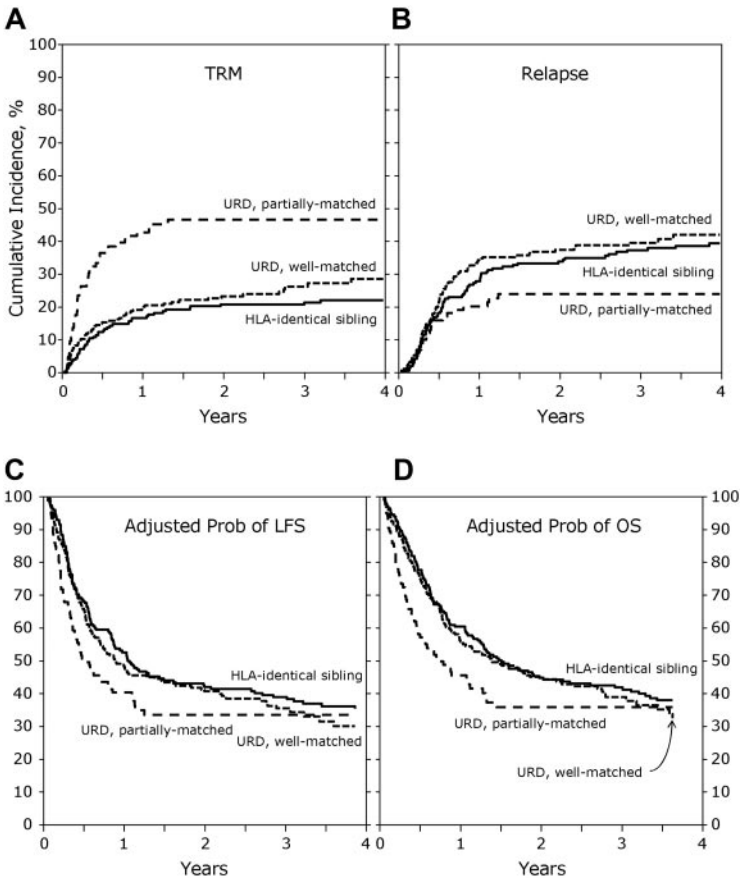

Figure 1. Comparisons of MSD, HLA-well-matched URD, and partially-matched URD transplantation in AML patients in CR1 with unfavorable cytogenetics. (A) Cumulative incidence of TRM. (B) Cumulative incidence of relapse. (C) Adjusted probability of LFS. (D) Adjusted probability of OS.

HCT. These findings are similar to a recent CIBMTR study demonstrating that the graft-versus-leukemia effect using URD is not superior to MSD for HCT.[29]

Caution needs to be exercised in the interpretation of these data because of limitations in retrospective observational registry analyses. Although patients were categorized by their disease biology and the multivariate modeling may have adjusted for various patient-, disease-, and transplantation-related factors, there may be factors of importance that we have not been able to take into account. For example, it is possible that inherent selection exists such that lesser fit patients may not be referred for URD HCT; and of course, those with the highest risk may relapse before consideration of allografting during CR1.

In this study, unfavorable cytogenetics was defined according to the SWOG/ECOG classification.[22] Some abnormalities, such as del(7q), 9q, 11q, 20q, 21q, and 17p, defined as unfavorable in the SWOG/ECOG classification, are defined as intermediate risk in the Medical Research Council classification.[30] However, HCT during CR1 appears similarly effective for all unfavorable cytogenetically defined subsets. These data have to be interpreted with caution as some of the cytogenetics subsets were relatively small in size. Monosomal karyotype has recently been identified as an extremely poor prognosis abnormality.[31] Whether HCT can overcome the poor prognosis associated with monosomal karyotype is not known. Lacking central cytogenetic review, we were unable to address this question directly.

Unexpectedly, TRM was increased with the use of myeloid growth factors to promote engraftment. A retrospective study from European Blood and Marrow Transplant Group had shown increased acute GVHD, chronic GVHD, and TRM in the recipients of BM grafts, where growth factors were used to promote engraftment.[32] However, a study from CIBMTR and meta-analysis of prospective trials did not show any differences in GVHD or TRM.[33,34] In our study, the cause of increased TRM with use of growth factors is not clear but might be related to use of growth factors in older, previously infected, or sicker patients. Additional data were not available for a more detailed analysis of these questions.

Patients who were older than 50 years and received RIC regimens had a higher risk of relapse and inferior LFS and OS compared with those who received myeloablative regimens. We further investigated whether the difference in relapse could be related to a higher proportion of patients 60 years of age or older in the RIC cohort. The relapse rate was similar after excluding the patients 60 years of age or older (data not shown), but other factors inherent in each center's decision to assign RIC may have contributed to these observed poorer outcomes. Caution is essential in the interpretation of these results as the study was not designed to compare the intensity of the conditioning regimens.

In conclusion, LFS and OS after either well-matched URD or MSD HCT are similar for AML CR1 with unfavorable cytogenetics. We suggest that, if a suitable MSD is not available, HLA-well-matched URD HCT is appropriate in high-risk AML during CR1. Our study supports the inclusion of URD HCT in the trial designs of prospective studies evaluating various postremission strategies for patients with high-risk AML.

Table 3. Multivariate analysis of TRM and relapse

	n	Relative risk (95% CI)	*P*
TRM			
Donor type			< .001
Matched sibling	212	1.00	
URD, well-matched	249	1.55 (1.02-2.37)*	
URD, partially-matched	99	3.03 (1.94-4.75)*	
GVHD prophylaxis			.002
CsA ± other	277	1.00	
Tac ± other	225	0.48 (0.31-0.72)*	
T-cell depletion	46	1.07 (0.61-1.88)	
Other/missing	12	2.38 (0.95-5.99)	
Prior MDS			
No	452	1.00	
Yes	108	1.63 (1.11-2.41)	.01
Growth factor used to promote engraftment			
No	283	1.00	
Yes	184	1.70 (1.17-2.47)*	.005
Missing	93	1.09 (0.65-1.82)	
Graft type			
In first 3 mo after treatment			
BM	228	1.00	
PBPC	332	0.55 (0.32-0.95)	.03
After 3 mo after treatment			
BM	174	1.00	
PBPC	272	1.16 (0.70-1.94)	.561
Age and conditioning regimen			
In first 3 mo after treatment			.6
20-50 y, myeloablative	252	1.00	
Less than 20 y, myeloablative	84	0.61 (0.3-1.26)	
More than 50 y, myeloablative	82	0.63 (0.28-1.43)	
50 y or less, RIC	34	0.81 (0.25-2.69)	
More than 50 y, RIC	108	0.76 (0.37-1.57)	
After 3 mo after treatment			< .001
20-50 y, myeloablative	204	1.00	
Less than 20 y, myeloablative	68	0.34 (0.12-0.99)*	
More than 50 y, myeloablative	69	2.66 (1.50-4.73)*	
50 y or less, RIC	29	1.15 (0.4-3.32)	
More than 50 y, RIC	76	2.84 (1.55-5.23)*	
Relapse			
Donor type			.5
Matched sibling	212	1.00	
URD, well-matched	249	1.04 (0.76-1.42)	
URD, partially-matched	99	0.78 (0.48-1.24)	
Donor-recipient sex match			.002
Male-male	204	1.00	
Male-female	152	0.66 (0.47-0.94)*	
Female-male	108	0.48 (0.31-0.73)*	
Female-female	96	0.6 (0.39-0.92)*	
Age and conditioning regimen			< .001
20-50 y, myeloablative	252	1.00	
Less than 20 y, myeloablative	84	1.13 (0.73-1.73)	
More than 50 y, myeloablative	82	1.3 (0.81-2.08)	
50 y or less, RIC	34	1.3 (0.7-2.4)	
More than 50 y, RIC	108	3.08 (1.96-4.83)*	
Acute GVHD			
No	288	1.00	
Yes	272	0.99 (0.74-1.33)	.96
Chronic GVHD			
No	331	1.00	
Yes	229	0.68 (0.47-0.99)	.046

In each comparison group, *P* values reflect an overall significant difference between the groups. Because of interactions between age and conditioning regimen as well as nonproportional hazards over time, TRM was analyzed by time periods as shown.

Tac indicates tacrolimus; and BM, bone marrow.

*Significantly different value from the reference group.

Table 4. Multivariate analysis of LFS and OS

Variable	n	Relative risk (95% CI)	*P*
LFS			
Donor type			.114
Matched sibling	212	1.00	
URD, well-matched	249	1.10 (0.86-1.40)	
URD, partially-matched	99	1.38 (1.02-1.87)*	
Prior MDS			
No	452	1.00	
Yes	108	1.42 (1.10-1.84)	.007
Graft type			
In first 3 mo after treatment			
BM	228	1.00	
PBPC	332	0.6 (0.39-0.91)	.016
After 3 mo after treatment			
BM	174	1.00	
PBPC	272	0.96 (0.71-1.3)	.8
Age and conditioning regimen			
In first 3 mo after treatment			.072
20-50 y, myeloablative	252	1.00	
Less than 20 y, myeloablative	84	0.78 (0.43-1.41)	
More than 50 y, myeloablative	82	0.86 (0.46-1.59)	
50 y or less, RIC	34	0.85 (0.33-2.14)	
More than 0 y, RIC	108	1.75 1.08-2.83)*	
After 3 mo after treatment			< .001
20-50 y, myeloablative	204	1.00	
Less than 20 y, myeloablative	68	0.88 (0.57-1.36)	
More than 50 y, myeloablative	69	1.7 (1.17-2.47)*	
50 y or less, RIC	29	1.22 (0.69-2.16)	
More than 0 y, RIC	76	2.56 (1.78-3.69)*	
Acute GVHD (grade 2-4, time-dependent)			
No	288	1.00	
Yes	272	1.53 (1.23-1.9)	< .001
Chronic GVHD (time-dependent)			
No	331	1.00	
Yes	229	1.11 (0.83-1.48)	.48
OS			
Donor type			.07
Matched sibling	216	1.00	
URD, well-matched	251	1.06 (0.83-1.37)	
URD, partially-matched	101	1.42 (1.04-1.94)*	
Therapy-related leukemia			
No	487	1.00	
Yes	81	1.44 (1.07-1.95)	.017
Donor-recipient sex match			
Male-male	207	1.00	.029
Male-female	153	0.67 (0.5-0.89)*	
Female-male	109	0.74 (0.55-1.01)*	
Female-female	99	0.78 (0.56-1.06)	
Graft type			
In first 3 mo after treatment			
BM	231	1.00	
PBPC	337	0.51 (0.31-0.83)	.006
After 3 mo after treatment			
BM	187	1.00	
PBPC	300	0.94 (0.71-1.26)	.7
Age and conditioning regimen			
In first 3 mo after treatment			.5
20-50 y, myeloablative	254	1.00	
Less than 20 y, myeloablative	85	0.68 (0.35-1.32)	
More than 50 y, myeloablative	85	0.7 (0.34-1.44)	
50 y or less, RIC	35	0.61 (0.19-2.16)	
More than 50 y, RIC	109	1.15 (0.63-2.11)	5

In each comparison group, *P* values reflect an overall significant difference between the groups. Because of interactions between age and conditioning regimen as well as nonproportional hazards over time, TRM was analyzed by time periods as shown.

BM indicates bone marrow.

*Significantly different value from the reference group.

Table 4. Multivariate analysis of LFS and OS (continued)

Variable	n	Relative risk (95% CI)	*P*
After 3 mo after treatment			< .001
20-50 y, myeloablative	214	1.00	
Less than 20 y, myeloablative	73	0.88 (0.58-1.34)	
More than 50 y, myeloablative	76	1.82 (1.27-2.6)*	
50 y or less, RIC	32	1.19 (0.68-2.07)	
More than 50 y, RIC	92	2.88 (2.05-4.04)*	
Acute GVHD (grade 2-4, time-dependent)			
No	287	1.00	
Yes	275	1.78 (1.42-2.22)	< .001
Chronic GVHD (time-dependent)			
No	327	1.00	
Yes	230	0.91 (0.69-1.20)	.5

In each comparison group, *P* values reflect an overall significant difference between the groups. Because of interactions between age and conditioning regimen as well as nonproportional hazards over time, TRM was analyzed by time periods as shown.

BM indicates bone marrow.

*Significantly different value from the reference group.

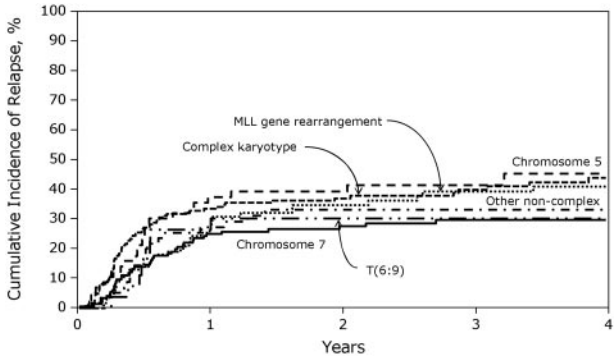

Figure 2. Impact of various unfavorable cytogenetic subsets on relapse.

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Authorship

Contribution: V.G., M.S.T., and D.J.W. designed the study, interpreted the data, and prepared the manuscript; W.H. and B.R.L. performed statistical analysis; and E.C., R.P.G., H.J.K., T.K., J.K., H.M.L., D.I.M., R.M., D.A.R., J.M.R., M.S., E.W., J.F.D., and D.W.B. interpreted the data and approved the final manuscript.

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